



Normandie Université



COMORBIDITIES AND OVERLAP SYNDROMES IN FUNCTIONAL DYSPEPSIA

Comorbidités et syndromes de
chevauchement dans la dyspepsie
fonctionnelle

Fabien WUESTENBERGHS

PhD thesis / Thèse de doctorat

H. Piessevaux & G. Gourcerol, directors

2017-2023



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A la mémoire de mon grand-père, Théophile

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THÈSE EN COTUTELLE INTERNATIONALE AVEC LABEL DE DOCTORAT EUROPÉEN

en vue de l'obtention des grades de Docteur en

Sciences médicales / Sciences de la Vie et de la Santé

préparée au sein de l'Université catholique de Louvain
et de l'Université de Rouen Normandie,
au sein du laboratoire INSERM UMR 1073 dirigé par le Prof. Pierre
Déchelotte (2017-2021) puis par le Prof. Moïse Coëffier (2022-)

Comorbidités et syndromes de chevauchement dans la dyspepsie fonctionnelle

Présentée et soutenue par
Fabien WUESTENBERGHS

devant un jury composé de		
Mme Maura CORSETTI	Université de Nottingham 	Rapporteuse et Examinatrice
M. Pierre DÉCHELOTTE	Univ. Rouen Normandie 	Examinateur
M. Heiko DE SCHEPPER	Université d'Anvers 	Examinateur
M. Guillaume GOURCEROL	Univ. Rouen Normandie 	Co-directeur de thèse
Mme Isabelle LECLERCQ	UCLouvain 	Présidente et Examinatrice
M. Hubert PIESSEVAUX	UCLouvain 	Directeur de thèse et Secrétaire
M. Andreas STENGEL	Université Eberhard Karl de Tübingen 	Rapporteur et Examinateur
M. Jan TACK	KU Leuven 	Examinateur

Thèse dirigée par
Hubert PIESSEVAUX & Guillaume GOURCEROL

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Doctoral schools

Norman Doctoral School of Integrative Biology, Health, Environment 497 (EdNBISE 497), Normandie Univ, UNIROUEN, France

Doctoral school of the Health Sciences Sector, UCLouvain, Belgium

THESIS IN INTERNATIONAL COTUTELLE WITH EUROPEAN LABEL

to obtain the degrees of Doctor of Philosophy (PhD) in

Medical Sciences / Life and Health Sciences

prepared at the Université catholique de Louvain
and at the Université de Rouen Normandie,
in the laboratory INSERM UMR 1073, directed by Prof. Pierre
Déchelotte (2017-2021), followed by Prof. Moïse Coëffier (2022-)

Comorbidities and overlap syndromes in functional dyspepsia

Presented and defended by
Fabien WUESTENBERGHS

in front of a jury composed of		
Maura CORSETTI	University of Nottingham 	Reviewer & Examiner
Pierre DÉCHELOTTE	Univ. Rouen Normandie 	Examiner
Heiko DE SCHEPPER	Universiteit Antwerpen 	Examiner
Guillaume GOURCEROL	Univ. Rouen Normandie 	Co-director
Isabelle LECLERCQ	UCLouvain 	President
Hubert PIESSEVAUX	UCLouvain 	Director & Secretary
Andreas STENGEL	Eberhard Karls Universität Tübingen 	Reviewer & Examiner
Jan TACK	KU Leuven 	Examiner

Thesis directed by
Hubert PIESSEVAUX & Guillaume GOURCEROL

Thèse présentée à la Faculté de médecine et médecine dentaire (MEDE) de l'Université catholique de Louvain (université accueillant la soutenance) en vue de l'obtention du grade de Docteur en Sciences médicales.
Secteur des Sciences de la Santé (SSS), UCLouvain, Belgique

A thesis submitted to the Faculty of Medicine and Dentistry (MEDE) of the Catholic University of Louvain (university hosting the defence) in partial fulfilment of the requirements for the *Philosophiae Doctor* (PhD) degree in Medical Sciences.
Health Sciences Sector, UCLouvain, Belgium

Le doctorant a rempli les conditions requises pour l'attribution du label européen à son diplôme de doctorat lors de la préparation de sa thèse et de l'obtention de son diplôme.

The PhD student has fulfilled the conditions required for the attribution of the European label for his doctoral degree during the preparation of his thesis and upon obtaining his diploma.



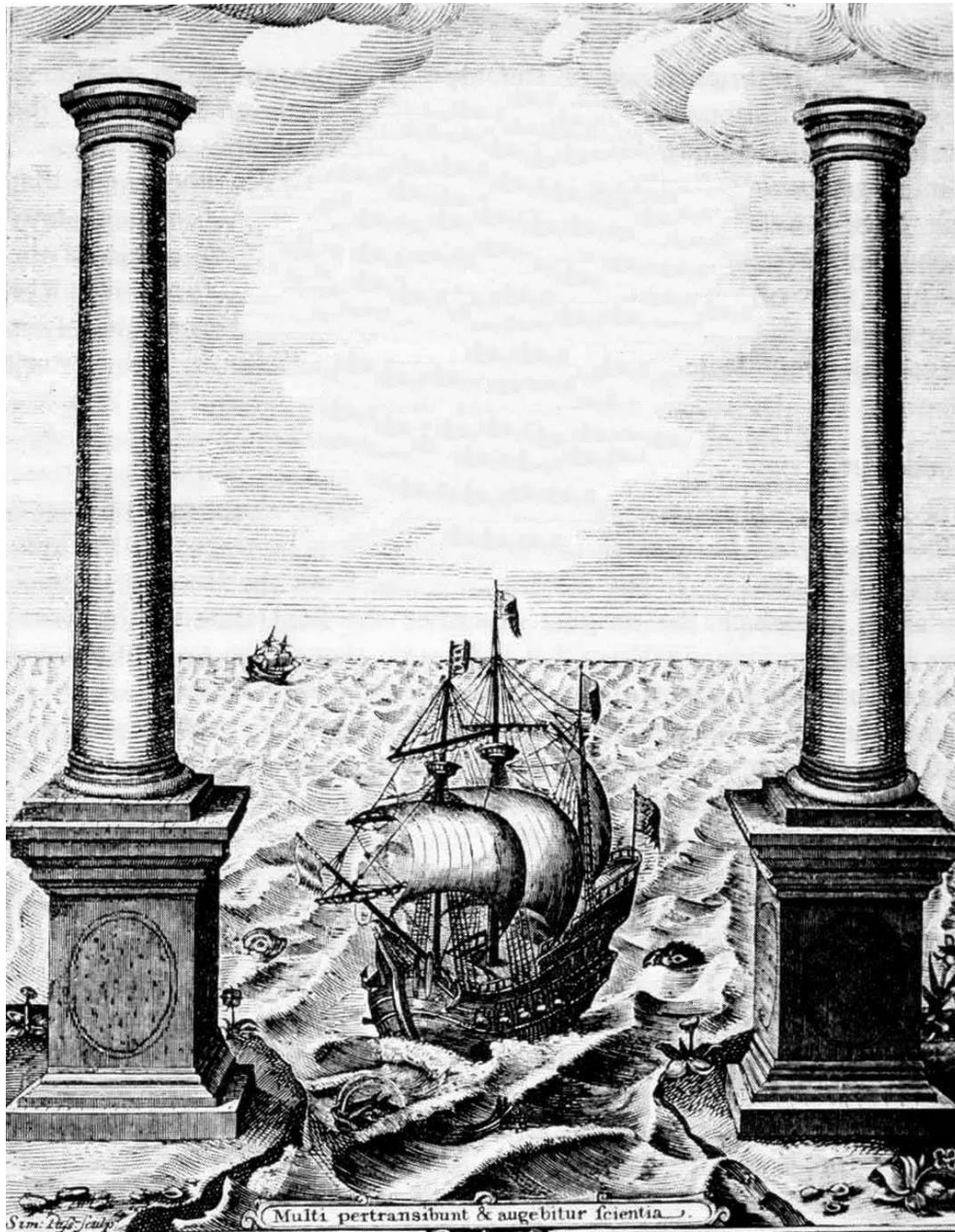
La défense privée a eu lieu le 19 décembre 2022 entre 12h00 et 15h00 dans la bibliothèque du service de gastroentérologie des Cliniques universitaires Saint-Luc à Louvain-en-Woluwe, Belgique.

The private defence took place on December 19, 2022, between 12:00 p.m. and 3:00 p.m. at the library of the Department of gastroenterology of Saint-Luc University Hospital, Louvain-en-Woluwe, Belgium.

La soutenance publique est prévue ce 17 avril 2023 entre 16h00 et 18h00 dans l'auditoire 38A du Pavillon des Conférences à Louvain-en-Woluwe, Belgique.

The public defence is scheduled for April 17, 2023, between 4:00 p.m. and 6:00 p.m. in the auditorium 38A of the Pavillon des Conférences in Louvain-en-Woluwe, Belgium.

Adapted from the frontispiece of the original edition of the
Novum Organum (Francis Bacon, 1620)



Multi pertransibunt et augebitur scientia

"Many will travel, and knowledge will be increased."

« Beaucoup voyageront en tous sens et feront progresser la Science. »

Old Testament: Daniel 12:4

Affidavit

Je, soussigné Fabien WUESTENBERGHS, déclare par la présente que les travaux de recherche présentés dans ce manuscrit et la rédaction de celui-ci sont mon travail propre, réalisé sous la direction scientifique de M. Hubert PIESSEVAUX (directeur de thèse) et de M. Guillaume GOURCEROL (co-directeur de thèse) au sein des unités de recherche « GAEN » (IREC) et « Nutrition, inflammation et axe microbiote-intestin-cerveau » (IRIB), dans le respect des principes de fiabilité, d'honnêteté, de respect, de responsabilité et d'esprit critique inhérents aux bonnes pratiques en matière de recherche.

Je souscris au Code européen d'intégrité scientifique (All European Academies, 2013) et à la Déclaration de Singapour pour l'intégrité de la recherche (World Conference on Research Integrity, 2010). En obtenant le diplôme de doctorat, je m'engage à agir également à l'avenir conformément aux principes de l'intégrité en recherche.

Le contenu de ce manuscrit (y compris les parties publiées) a fait l'objet d'une vérification de plagiat à l'aide de l'outil Compilatio Magister et a obtenu un score de 11%.

Je n'ai pas de conflit d'intérêt financier en lien avec les travaux de ma thèse. Celle-ci a été financée partiellement par la Fondation Mont-Godinne.

Fait à Yvoir, le 9 septembre 2022

Fabien Wuestenberghs



Affidavit

I, the undersigned Fabien WUESTENBERGHS, hereby declare that the research work presented in this manuscript and the writing of it are my own work, carried out under the scientific direction of Mr. Hubert PIESSEVAUX (thesis director) and Mr. Guillaume GOURCEROL (thesis co-director) within the "GAEN" (IREC) and "Nutrition, inflammation and microbiota-gut-brain axis" (IRIB) research units, respecting the principles of reliability, honesty, respect, accountability and critical thinking inherent in good research practices.

I subscribe to The European Code of Conduct for Research Integrity (All European Academies, 2013) and the Singapore Statement on Research Integrity (World Conference on Research Integrity, 2010). By obtaining the doctoral degree, I commit myself to act also in the future in accordance with the principles of research integrity.

The content of this manuscript (including published parts) was checked for plagiarism using Compilatio Magister tool and obtained a score of 11%.

I have no financial conflict of interest related to my thesis work. The Fondation Mont-Godinne partially funded this.

Yvoir, September 9, 2022

Fabien Wuestenberghs



Avant-propos – Foreword

J'ai rédigé mon manuscrit de thèse au format de « thèse sur articles ». Cette thèse sur publications a donc une forme mixte avec des chapitres d'introduction, de méthodologie et de discussion entrecoupés d'articles. Leur enchaînement met en exergue la démarche menée au cours du doctorat pour atteindre les objectifs fixés. Une dérogation afin de rédiger en langue anglaise a été accordée par ma convention de cotutelle. Un résumé substantiel écrit en français complète donc le manuscrit.

Une partie des travaux de recherche originaux réalisés lors de cette thèse, dont je suis l'auteur principal, ont été publiés ou soumis dans des revues à comité de lecture reconnues dans le domaine de la neurogastroentérologie et de la gastro-entérologie, et indexés dans des bases de données bibliographiques (MEDLINE [consultable via l'interface web PubMed[®]], Science Citation Index [accessible via la plateforme Web of Science[™]], Scopus...). Les articles 1 et 7 n'ont pas encore été soumis au moment de la publication du manuscrit de thèse.

L'utilisation du contenu des articles publiés dans des revues scientifiques et la réutilisation de figures déjà publiées sont conformes aux droits de diffusion prévus dans les contrats établis avec les éditeurs desdites revues et à la pratique académique acceptée. Le dépôt et la diffusion des articles scientifiques ainsi que du manuscrit de thèse respectent la réglementation en vigueur en Belgique et en France. Les droits des co-auteurs ont été respectés.

Les chapitres correspondant à des articles soumis ou publiés contiennent les textes desdits articles. La langue anglaise (anglais britannique), la mise en page du texte et de ses titres ainsi que la numérotation des figures et des tables ont été harmonisés dans tout le manuscrit. Les éventuelles erreurs et fautes de frappe ont été corrigées le cas échéant. Les abréviations ne sont détaillées que la première fois qu'elles apparaissent dans le manuscrit ; un chapitre sur les abréviations peut être consulté si nécessaire. Les références de tous les chapitres sont fusionnées en un seul paragraphe de bibliographie qui utilise le style Harvard. L'anglais a été corrigé à l'aide de l'assistant de frappe basé sur l'intelligence artificielle *Grammarly* pour Windows[®] (version 1.0.23.347, Grammarly, Inc., San Francisco, CA 94104, USA, [grammarly.com](https://www.grammarly.com)), combinant les technologies de traitement du langage naturel et d'apprentissage automatique.



I wrote my thesis manuscript in the format of a “thesis of articles”. This thesis of publications, therefore, takes a mixed form, with chapters of introduction, methodology and discussion interspersed with scientific articles. Their sequence highlights the approach taken during the PhD to achieve the objectives set. I was granted a derogation to write in English due to my agreement for joint supervision. An executive summary written in French, therefore, completes the manuscript.

Part of the original research work carried out during this thesis, of which I am the primary author, has been published submitted in recognised peer-reviewed journals in the field of neurogastroenterology and gastroenterology, and indexed in bibliographic databases (MEDLINE [available *via* the PubMed® web interface], Science Citation Index [available *via* the Web of Science™ platform], Scopus, etc.). Articles 1 and 7 have not yet been submitted at the time of sending the manuscript.

The use of the content of articles published in scientific journals and the reuse of figures already published comply with the copyrights provided for in the contracts established with the publishers of these journals, and with accepted academic practice. The submission and distribution of scientific articles and the thesis manuscript comply with the regulations in force in Belgium and France. The rights of co-authors have been respected.

The chapters corresponding to submitted or published articles contain the texts of those articles. The English language (British English), the layout of the text and its titles, as well as the numbering of figures and tables, have been harmonised throughout the manuscript. Any errors and typographic mistakes have been corrected where appropriate. Abbreviations are only detailed the first time they appear in the manuscript; an abbreviations chapter can be further referred to if necessary. The references from all chapters have been merged into a single bibliography using the Harvard style. English has been corrected using the artificial intelligence-based typing assistant *Grammarly* for Windows® (version 1.0.23.347, Grammarly, Inc., San Francisco, CA 94104, USA, [grammarly.com](https://www.grammarly.com)), combining natural language processing with machine learning technologies.



Remerciements – Acknowledgements

L'approche de la fin d'une thèse de doctorat est l'occasion de se remémorer toutes les étapes qui ont fini par aboutir à cet accomplissement et de remercier ceux qui y ont contribué. Mon intérêt pour les troubles fonctionnels digestifs a débuté fin 2014, alors que j'étais médecin assistant clinicien candidat spécialiste, lorsque j'ai eu l'opportunité de participer en tant que sous-investigateur au recrutement de patient·e·s pour la « LPDS/Itopride study » (Carbone et al., 2016), grâce au Professeur Thierry De Ronde puis au Docteur Philippe Warzée qui m'ont fait confiance en me déléguant le suivi des patient·e·s, mais aussi à celle de Madame Florencia Carbone, doctorante au *Translational Research Center for Gastrointestinal Disorders* (TARGID), et de son directeur de thèse, le Professeur Jan Tack. C'est alors que j'ai entendu parler pour la première fois de la dyspepsie fonctionnelle, maladie passée sous silence lors de nos cours de gastro-entérologie, et que le Docteur Alain Vandenberghe, consultant en recherche médicale, m'a fait découvrir pour pouvoir recruter les patient·e·s. C'était par la même occasion mon premier contact avec la recherche clinique. J'ai poursuivi ma formation dans le domaine en suivant le Diplôme Inter-Universitaire de « Pathologies Fonctionnelles Digestives » à l'Université Claude Bernard Lyon I, sous la responsabilité de la Professeure Sabine Roman, durant l'année académique 2015-2016. Lors de mon engagement au CHU UCL Namur l'année suivante, on m'a demandé de prendre en charge le secteur de physiologie digestive. Le souhait d'un stage de perfectionnement dans ce secteur m'a alors conduit en France grâce à mon collègue, le Docteur Abdenor Badaoui, qui connaissait le Professeur Philippe Ducrotté de l'Hôpital Charles Nicolle à Rouen, celui-ci ayant une renommée internationale en neurogastroentérologie. La prise de contact fût toutefois difficile ; j'ai appris par la suite qu'il luttait contre un cancer et je ne l'ai finalement rencontré qu'une seule fois lors d'une brève reprise de son activité hospitalière. C'est un de ses collègues, le Professeur Guillaume Gourcerol, qui m'a accueilli dans leur service de physiologie, alors dirigé par la Professeure Anne-Marie Leroi. A l'époque, je capitalisais mon « temps scientifique » pour y partir une semaine sur cinq afin de développer mes compétences dans la réalisation et l'interprétation des explorations fonctionnelles, ainsi que travailler sur des projets de recherche clinique. Lors

Remerciements

d'une entrevue avec le directeur aux affaires académiques de mon hôpital, le Professeur Maximilien Gourdin, celui-ci a lancé l'idée de prolonger mon stage de perfectionnement par une thèse de doctorat. Après réflexion et discussion avec mes collègues, notamment le Professeur Jean-François Rahier qui avait suivi le même parcours avant moi dans le domaine des maladies inflammatoires chroniques intestinales et m'avait mis en garde des sacrifices nécessaires dans une telle entreprise, j'ai pris ma décision et j'ai immédiatement reçu le soutien de mes collègues ainsi que du directeur médical de l'époque, le Professeur Yves Boutsen. J'en ai alors parlé avec le Professeur Gourcerol, qui a été soutenant dans ce projet, puis avec le Professeur Hubert Piessevaux qui est référent en neurogastroentérologie dans mon université de tutelle, l'UCLouvain, et qui a accepté de co-diriger la thèse. Je remercie chaleureusement mes deux directeurs de thèse pour leur soutien tout au long de ces 6 années ! La thèse n'aurait également pas pu avoir lieu sans l'aide de mes collègues, qui ont notamment pallié à mon absence à mi-temps liée à mon statut de spécialiste-doctorant, et que je remercie ici ; je pense surtout au Docteur Olivier Borgniet qui s'est régulièrement retrouvé seul sur le site de Dinant, mais aussi au Docteur Abdenor Badaoui dont les relations m'ont permis d'entrer en contact avec l'équipe rouennaise. Les patient·e·s dont je me suis occupé durant cette période ont également été mis·e·s à contribution ; organiser un suivi optimal avec mes absences répétées a été un challenge tout au long de la thèse. Un autre soutien important est venu de la Fondation Mont-Godinne, qui m'a octroyé une bourse afin de financer mes trajets et le logement à Rouen ; merci au Professeur André Bosly et à la secrétaire de la Fondation, Madame Carine Mahieux. Enfin, le Professeur Pierre Déchelotte m'a accueilli dans son laboratoire, l'unité mixte de recherche INSERM/Université 1073 (prononcez « dix soixante-treize ») alors que j'étais « naïf de labo » ; je le remercie de m'avoir fait confiance. La prise en charge des frais liés à l'activité au sein du laboratoire par celui-ci, et le maintien de mon salaire de médecin en ne dépassant pas la moitié de mon temps en recherche, ont complété le financement de ma thèse.

Beaucoup d'autres personnes ont été impliquées à des degrés divers tout au long de ces 5 années et je tiens à les remercier également. En particulier, Mathieu Meleine, qui avait été post-doctorant à l'U1073 avant moi, a fait le déplacement depuis Clermont-Ferrand pour m'apprendre les techniques de mesure de la sensibilité viscérale au niveau gastrique les 29 et 30 août 2017.

Karim Atmani, qui était alors en fin de thèse, a également été d'une grande aide pour m'insérer dans le laboratoire. Merci à vous deux.

Durant mes années aux laboratoires, j'ai cotoyé beaucoup de doctorant·e·s, qui étaient sur leur fin de thèse, sont arrivé·e·s après moi et ont terminé avant mon départ, ou sont toujours en train d'achever leur doctorat : Asma Amamou, Karim Atmani, Annabelle Aublé, Wafa Bahlouli, Charlotte Desprez, Manon Dominique, Virginie Dreux, Chaïma Ezzine, Marie Galmiche, Mathilde Leboutte, Candice Lefebvre, Clément L'Huillier (qui a longtemps partagé le bureau adjacent au mien), Axelle Liebaut, Léa Loison, Robin Louail (expert ès fèces), Chloé Melchior, Séverine Nobis, Adrien Noël, Emmeline Salameh, Colin Salaün, Heithem Soliman, Kuniko Takagi, Pauline Tirelle... Mais également les post-doctorants Jonathan Breton et Ludovic Langlois, l'équipe « Targedys », Romain Legrand et Nicolas Lucas, les techniciennes du laboratoire, Christine Bôle-Feysot, Charlène Guerin, Alice Beau, Illona Bouleté, Camille Deroissart, Marine Jarbeau, Marie-Anne Le Sollic, l'équipe encadrante composée du Professeur Moïse Coëffier, du Professeur Pierre Déchelotte, du Docteur Alexis Goichon, de la Docteure Rachel Marion-Letellier, du Docteur David Ribet, de la Professeure Najate Achamrah, du Professeur Sergueï Fetissov, et de la Docteure Liliana Belmonte, les secrétaires, Mesdames Sylvie Martins et Sabine Douville, sans oublier Evelyne, la technicienne de surface de l'unité. Je remercie le Professeur Paul Mulder pour son aide lors de la soumission de la saisine, le responsable de l'animalerie, Monsieur Yann Lacoume, les technicien·ne·s animalier·ère·s en laboratoire qui se sont occupé·e·s de mes rats, et en particulier Monsieur Ronald Huot, ainsi que le vétérinaire de l'animalerie, le Docteur Jean-François Guillemain, et la Docteure Valérie Bridoux pour m'avoir fourni le Vicryl 3-0 nécessaire à mes manipulations. Je remercie également Monsieur Gregory Mosni qui a été d'une grande aide au sein du service de physiologie, de même que Messieurs Alexis Deperrois et Christian Helluin.

Je remercie les membres de mon comité d'accompagnement à l'UCLouvain, la Professeure Isabelle Leclercq et les Professeurs Pierre Déchelotte, Jan Tack et Jean-Marie Maloteaux, de même que ceux de mon comité de suivi individuel de thèse à Rouen, la Docteure Malvyne Rolli-Derkinderen, Madame Bérénice Colleville, et les Professeurs Frank Le Foll et Jean-Marc Sabaté, d'avoir participé aux sessions et de m'avoir conseillé. Je remercie également Mesdames Sandrine Wollanders, Lynda Letêtu, Sandra Tamion et Emilie Despois, secrétaires

Remerciements

des écoles doctorales auxquelles j'étais inscrit, pour leur suivi tout au long de ces années.

Je remercie les co-auteur-e-s des publications pour leurs commentaires critiques lors des révisions des manuscrits des articles. Je remercie également Madame Nikki Sabourin-Gibbs et la société Proof-Reading-Service.com Ltd pour les corrections de l'anglais. Enfin, je remercie la Docteure Adeline Donati et le Professeur Frank Aboubakar Nana pour leurs relectures des parties « hors articles » de mon manuscrit de thèse.

Je remercie les rapporteur-euse de mon manuscrit de thèse, la Professeure Maura Corsetti et le Professeur Andreas Stengel, ainsi que les examinateurs·trice ayant participé à ma défense privée et ma soutenance publique de thèse, la Professeure Isabelle Leclercq, et les Professeurs Pierre Déchelotte, Heiko De Schepper et Jan Tack.

Mon activité à Rouen n'aurait pas été possible sans les logements successifs que j'ai trouvé, surtout via la plateforme Airbnb initialement, mais aussi grâce à Pauline Bertot et sa fille Caroline, dont j'ai occupé le studio vacant à la fin de ses études de médecine, à Benoit Rimbart et sa jeune épouse Marie Lancesseur, un couple d'internes en fin de formation et qui partaient en Amérique du Sud avant de débiter leur carrière de praticien, à Wafa et surtout à Chloé qui m'a laissé son appartement lors de son post-doctorat en Suède. Merci à elleux, ainsi qu'à mes colocataires, Diane Cazaux, Charlotte Emonet et Andy Benzi, qui ont dû subir mes horaires au laboratoire.

Enfin, la vie continue parallèlement à la thèse. Mes deux grand-mères sont malheureusement décédées durant cette période, j'ai déclassé mon ancienne Mazda 3 à cause d'une harde de sangliers lors d'un départ à Rouen un dimanche soir... mais j'ai aussi beaucoup appris sur moi-même, je suis devenu propriétaire et j'ai fait de belles rencontres. Merci au soutien de ma famille et de mes amis, et à la compréhension de ma moitié sur la fin de la thèse ; nous rattrapons mes absences répétées liées à mon éloignement !

Fabien Wuestenberghs

Yvoir, le 18 septembre 2022



Ma thèse en quelques date-clés

- 15/09/2017 : début officiel de la thèse (inscription UCLouvain)
- 09/10/2017 : 1^{er} jour au laboratoire U1073 en tant que doctorant
- 06/06/2018 : inscription validée auprès de Normandie Université
- 19/06/2019 : 1^{er} comité de suivi individuel (CSI) (Rouen + virtuel)
- 03/07/2019 : 1^{er} comité d'accompagnement (Bruxelles)
- Mars 2020 – Juin 2020 : interdiction de déplacement vers la France suite à la pandémie de COVID-19
- 08/09/2020 : 2^{ème} CSI (Rouen + virtuel)
- 13/10/2020 : « épreuve de confirmation »
- Février 2021 – Mai 2021 : interdiction de déplacement vers la France pour limiter la dispersion des variants du SARS-CoV2
- 13/07/2021 : 3^{ème} CSI (Rouen + virtuel)
- 05/10/2021 : première inscription en année dérogatoire (Rouen)
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Résumé de la thèse

La dyspepsie fonctionnelle est un trouble fonctionnel du tube digestif haut se manifestant par des difficultés de digestion et/ou des douleurs dans la région de l'estomac. Un ralentissement de la vidange de l'estomac et/ou une hypersensibilité à la distension de l'estomac sont retrouvés chez une partie des patients. Des comorbidités ou syndromes de chevauchement sont fréquemment retrouvés dans ce trouble: maladies organiques, problèmes psychologiques (troubles du sommeil...) et autres troubles fonctionnels, digestifs (syndrome de l'intestin irritable, syndrome de nausées/vomissements chroniques, ...) ou non (syndrome de vessie douloureuse). Après avoir fait la synthèse des connaissances actuelles dans ce domaine, nous avons évalué différentes comorbidités et leur impact sur ce trouble, et exploré les mécanismes impliqués dans ces associations. Nous avons montré que les comorbidités sont fréquentes et que la présence d'un syndrome de chevauchement est associée à des symptômes digestifs plus sévères, une plus grande détresse psychologique et une moins bonne qualité de vie dans ce trouble. Une association avec le syndrome de vessie douloureuse est décrite pour la première fois. Les symptômes dyspeptiques sont influencés par la vidange de l'estomac uniquement chez les patients qui ont une vidange très ralentie mais pas chez les autres. Enfin, un modèle animal a été développé chez le rat : une inflammation du colon induite par une substance chimique entraîne une hypersensibilité de l'estomac ; cette sensibilisation croisée est médiée par la microglie, des cellules présentes dans le système nerveux central, et est prévenue par l'administration d'un inhibiteur de ces cellules, la minocycline.



Abstract of the thesis

Functional dyspepsia is a functional disorder of the upper digestive tract manifested by indigestion and pain in the stomach region. Delayed emptying of the stomach and hypersensitivity to gastric distension are found in some patients. Comorbidities or overlap syndromes are frequently found in the disorder: organic diseases, psychological problems (sleep disorders, etc.) and other functional disorders, digestive (irritable bowel syndrome, chronic nausea and vomiting syndrome, etc.) or not (bladder pain syndrome). After synthesising current knowledge in this field, we assessed different comorbidities and their impact on this disorder, and explored the mechanisms involved in these associations. We have shown that comorbidities are frequent and that an overlap syndrome is associated with more severe digestive symptoms, greater psychological distress and poorer quality of life in this disorder. An association with bladder pain syndrome is first described. Dyspeptic symptoms are influenced by the emptying of the stomach only in patients with severely delayed emptying but not in others. Finally, an animal model has been developed in the rat: inflammation of the colon induced by a chemical substance leads to hypersensitivity of the stomach; this cross-sensitisation is mediated by microglia, cells present in the central nervous system, and is prevented by the administration of minocycline, an inhibitor of these cells.



Mots clés – Keywords

Comorbidités ; critères de Rome ; douleur ; douleur abdominale ; dyspepsie fonctionnelle ; hypersensibilité viscérale ; interaction neuro-gliale ; microglie ; qualité de vie ; sensibilisation croisée ; sommeil ; syndrome de l'intestin irritable ; syndrome de nausées et vomissements chroniques ; syndrome de vessie douloureuse ; syndromes de chevauchement ; troubles des interactions intestin-cerveau ; troubles fonctionnels intestinaux ; vidange gastrique ; viscéro-sensibilisation croisée.



Abdominal pain; bladder pain syndrome; comorbidities; chronic nausea and vomiting syndrome; cross-organ visceral sensitisation; cross-sensitisation; disorders of gut-brain interactions; functional dyspepsia; functional gastrointestinal disorders; gastric emptying; irritable bowel syndrome; microglia; neuro-glial interaction; overlap syndromes; pain; quality of life; Rome criteria; sleep; visceral hypersensitivity.





Mon bureau dans la pièce des doctorants à l'UMR 1073.



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- My professional status as a specialist-doctoral student was a full-time employee. My salary from CHU UCL Namur was my primary funding source.
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- The joint INSERM/University 1073 research unit took charge of the costs related to my activity within the laboratory (animals, consumables, technician time, etc.).
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Sommaire – Table of contents

Affidavit.....	I
Avant-propos – Foreword	III
Remerciements – Acknowledgements	V
Ma thèse en quelques date-clés	IX
Résumé de la thèse	XI
Abstract of the thesis	XII
Mots clés – Keywords	XIII
Laboratoire d’accueil – Host laboratory	XV
Laboratoire de rattachement – Home laboratory	XVI
Financement – Funding of the thesis.....	XVII
Sommaire – Table of contents	XIX
Liste des illustrations – List of figures	XXXI
Liste des tableaux – List of tables	XXXV
Glossaire – Abbreviations & acronyms	XXXIX
CHAPTER 1 INTRODUCTION	- 1 -
1.1. Disorders of gut-brain interactions: focus on functional dyspepsia	- 1 -
Definitions.....	- 2 -
Epidemiology.....	- 8 -
Pathophysiology.....	- 9 -
Diagnosis	- 14 -
Prognosis.....	- 15 -
Treatment	- 16 -
1.2. Main comorbidities associated with functional dyspepsia	- 18 -

Sommaire

Overlaps with organic diseases.....	- 19 -
Overlaps with other disorders of gut-brain interactions	- 28 -
Overlaps with non-gastrointestinal functional somatic disorders.....	- 33 -
Overlaps with psychological factors and psychiatric conditions	- 39 -
1.3. Pathophysiology of overlaps in functional dyspepsia.....	- 43 -
1.4. Pain and visceral nociception.....	- 48 -
Pain.....	- 48 -
Anatomy of gut nociception	- 49 -
Pain perception.....	- 58 -
Gut perception & visceral nociceptive signalling.....	- 59 -
Visceral hypersensitivity	- 61 -
1.5. Cross-organ sensitisation	- 65 -
Cross-organ visceral sensitisation.....	- 65 -
Example: cross-sensitisation between pelvic organs.....	- 69 -
1.6. Role of microglia in visceral sensitivity processes	- 71 -
1.7. Cross-organ sensitisation between the upper and lower gastrointestinal tracts: state of the art	- 75 -
Evidence in animals.....	- 76 -
Evidence in humans	- 77 -
1.8. Summary	- 79 -
CHAPTER 2 RESEARCH OBJECTIVES.....	- 81 -
CHAPTER 3 ARTICLE 1. SYSTEMATIC REVIEW WITH META-ANALYSIS OF COMORBIDITIES AND OVERLAP SYNDROMES IN FUNCTIONAL DYSPEPSIA.....	- 83 -
3.1. Introductory paragraph	- 83 -
3.2. Title page.....	- 85 -
3.3. Abstract.....	- 87 -

3.4. Introduction	- 89 -
3.5. Methods	- 89 -
Search strategy	- 90 -
Selection criteria	- 90 -
Data extraction & quality assessment	- 91 -
Data analysis & synthesis	- 91 -
3.6. Results	- 91 -
Overlaps with organic diseases	- 94 -
Overlaps with other disorders of gut-brain interactions	- 100 -
Overlaps with non-gastrointestinal functional somatic syndromes	- 104 -
Overlaps with psychological factors	- 106 -
Associations of comorbidities with FD compared to controls	- 111 -
3.7. Discussion	- 138 -
What have we learned from our work?	- 138 -
What does it teach us about the pathophysiology of functional dyspepsia?	- 139 -
What are the gaps in knowledge about comorbidities and overlap syndromes in functional dyspepsia?	- 139 -
3.8. Conclusion	- 139 -
3.9. Concluding paragraph	- 141 -
CHAPTER 4 METHODS USED FOR CLINICAL PROJECTS	- 143 -
4.1. Diagnosis and phenotyping of disorders of gut-brain interactions	- 143 -
4.2. Assessment of symptom burden in disorders of gut-brain interactions	- 145 -
4.3. Assessment of comorbidities in disorders of gut-brain interactions	- 146 -
4.4. Assessment of quality of life in disorders of gut-brain interactions	- 148 -

Sommaire

4.5. Assessment of gastric emptying	- 149 -
CHAPTER 5 ARTICLE 2. STUDY OF SLEEP DISTURBANCE AND QUALITY OF LIFE IN FUNCTIONAL DYSPEPSIA	- 157 -
5.1. Introductory paragraph	- 157 -
5.2. Title page.....	- 159 -
5.3. Abstract.....	- 161 -
5.4. Introduction	- 163 -
5.5. Materials and methods.....	- 163 -
Patients	- 164 -
Diagnostic criteria and assessment of patients' characteristics	- 164 -
Evaluation of sleep.....	- 165 -
Study design & statistical analysis	- 165 -
5.6. Results.....	- 166 -
Patient characteristics.....	- 166 -
Comparison between patients with and without sleep quality impairment.....	- 169 -
Comparison between patients with and without insomnia	- 172 -
Factors predicting altered sleep quality and insomnia in patients with functional dyspepsia	- 172 -
5.7. Discussion.....	- 173 -
5.8. Conclusion.....	- 176 -
5.9. Concluding paragraph	- 179 -
CHAPTER 6 ARTICLE 3. FUNCTIONAL DYSPEPSIA VS CHRONIC NAUSEA AND VOMITING SYNDROME... THE SAME ENTITY OR TWO?	- 181 -
6.1. Introductory paragraph	- 181 -
6.2. Title page.....	- 183 -
6.3. Abstract.....	- 185 -

6.4. Introduction	187 -
6.5. Materials and methods.....	188 -
Patients	188 -
Assessment of patients' characteristics.....	189 -
Study description	190 -
Statistical analysis	191 -
6.6. Results.....	191 -
Patients' characteristics	191 -
Comparison of patients' characteristics according to groups	192 -
Comparison of symptom patterns between the four groups.....	196 -
Predictors of overlap with chronic nausea and vomiting syndrome among patients with functional dyspepsia	198 -
Assessment of gastric emptying and a cut-off for vomiting in a subset of patients	199 -
6.7. Discussion.....	200 -
6.8. Conclusion.....	202 -
6.9. Concluding paragraph	203 -
CHAPTER 7 ARTICLE 4. LINK BETWEEN GASTRIC EMPTYING, SYMPTOM BURDEN, AND QUALITY OF LIFE IN DYSPEPSIA	205 -
7.1. Introductory paragraph	205 -
7.2. Title page.....	207 -
7.3. Abstract.....	209 -
7.4. Introduction	211 -
7.5. Materials and methods.....	211 -
Patients	212 -
Evaluation of symptoms and quality of life	212 -

Sommaire

Gastric emptying assessment	213 -
Study description	213 -
Statistical analysis	214 -
7.6. Results.....	214 -
Patient characteristics and their correlation with gastric emptying	214 -
Comparison between patients with a $T_{1/2} \leq 166$ min and > 166 min	216 -
Comparison between patients with a $T_{1/2} \leq 200$ min and > 200 min	218 -
Re-analysis of the data over 4 hours vs > 6 hours	221 -
7.7. Discussion.....	222 -
7.8. Conclusion.....	226 -
7.9. Concluding paragraph	227 -
CHAPTER 8 ARTICLE 5. ASSESSMENT OF OVERLAPS WITH BLADDER PAIN SYNDROME AND IRRITABLE BOWEL SYNDROME IN FUNCTIONAL DYSPEPSIA.....	229 -
8.1. Introductory paragraph	229 -
8.2. Title page.....	231 -
8.3. Abstract.....	233 -
8.4. Introduction	235 -
8.5. Materials and methods.....	236 -
Patients	236 -
Diagnostic criteria	236 -
Symptom questionnaires	237 -
Gastric emptying.....	237 -
Study design.....	238 -
Statistical analysis	238 -
8.6. Results.....	239 -
Patient characteristics.....	239 -

Prevalence of bladder pain syndrome in patients with functional dyspepsia....	- 243 -
Differences between diagnostic groups	- 243 -
Subgroup analysis of gastric emptying	- 247 -
8.7. Discussion.....	- 247 -
8.8. Conclusion.....	- 250 -
8.9. Concluding paragraph	- 251 -
CHAPTER 9 METHODS USED FOR EXPERIMENTAL PROJECTS	- 253 -
9.1. Animal models of visceral hypersensitivity.....	- 253 -
9.2. Animal models of cross-organ visceral sensitisation	- 257 -
9.3. Study of visceral sensitivity	- 259 -
Distensions of the gastrointestinal tract & pseudo-affective reflexes	- 259 -
Neurophysiological tests	- 262 -
Measurement of autonomic dysfunction	- 263 -
Functional brain imaging.....	- 263 -
Other methods.....	- 264 -
9.4. Study of intestinal permeability.....	- 265 -
Intestinal epithelial barrier	- 265 -
Alterations of gut barrier in disorders of gut-brain interactions	- 266 -
Methods to assess gut permeability.....	- 267 -
CHAPTER 10 ARTICLE 6. DEVELOPMENT OF A CHRONIC BLADDER-COLON CROSS-SENSITISATION MODEL IN MICE	- 271 -
10.1. Introductory paragraph	- 271 -
10.2. Title page.....	- 273 -
10.3. Abstract.....	- 275 -
10.4. Introduction	- 277 -

Sommaire

10.5. Materials and methods.....	- 278 -
Ethics.....	- 278 -
Animals.....	- 278 -
Study design.....	- 278 -
Acetic acid sensitisation.....	- 279 -
Colorectal distension and visceral sensitivity measurement.....	- 279 -
Measurement of bladder and colonic paracellular permeabilities	- 280 -
Myeloperoxidase measurement.....	- 280 -
c-Fos immunofluorescence.....	- 281 -
Semiquantitative PCR for the detection of TNF- α , IL-1 β and IL-10 mRNA in the spinal cord.....	- 282 -
Analysis of microglial cells.....	- 282 -
Pharmacologic studies	- 283 -
Western blot analysis.....	- 283 -
Statistics.....	- 284 -
10.6. Results.....	- 284 -
Development and validation of a mouse model of chronic bladder-colon cross-sensitisation.....	- 284 -
Permeability and inflammatory parameters of bladder and colon	- 287 -
Neural activation in the dorsal horn of the spinal cord L6-S1	- 288 -
Implication of central microglia from the dorsal horn of the spinal cord L6-S1 in bladder-colon cross-sensitisation	- 289 -
Involvement of central NK1R in bladder-colon cross-sensitisation.....	- 292 -
Assessment of the expression of spinal pro- and anti-inflammatory transcripts	- 295 -
10.7. Discussion.....	- 296 -
10.8. Conclusion.....	- 300 -

10.9. Concluding paragraph	301 -
CHAPTER 11 ARTICLE 7. DEVELOPMENT OF A CHRONIC COLON-STOMACH CROSS-SENSITISATION MODEL IN RATS	303 -
11.1. Introductory paragraph	303 -
11.2. Title page.....	305 -
11.3. Abstract.....	307 -
11.4. Introduction	309 -
11.5. Methods.....	309 -
Ethical statement	309 -
Animals.....	310 -
Experimental protocols.....	310 -
Chemical colitis	311 -
Assessment of visceral sensitivity	311 -
Pharmacologic studies	313 -
Assessment of tissue inflammation	313 -
Cytokine measurements on plasma.....	314 -
Semi-quantitative reverse transcription polymerase chain reaction (sqRT-qPCR) for the detection of TNF- α , IL-1 β and IL-10 messenger RNA (mRNA) in the spinal cord.....	315 -
Western blot analysis.....	316 -
Measurement of gastric and colonic paracellular permeabilities	317 -
Statistical analysis	318 -
11.6. Results.....	318 -
Baseline data of the first series.....	318 -
Inflammatory parameters and permeability assessment.....	318 -
Development of the rat model of colon-stomach cross-sensitisation.....	321 -

Sommaire

Implication of central microglia in colon-stomach cross-sensitisation.....	322 -
Involvement of central phosphorylated MAPK-p38 in colon-stomach cross-sensitisation	324 -
Assessment of the expression of spinal pro- and anti-inflammatory cytokines.	325 -
Participation of central NK1R in colon-stomach cross-sensitisation	326 -
11.7. Discussion.....	326 -
11.8. Conclusion.....	329 -
11.9. Concluding paragraph.....	331 -
CHAPTER 12 GENERAL DISCUSSION	333 -
12.1. Overview of the results.....	333 -
12.2. Directions for future research.....	344 -
Clinical research	344 -
Experimental research	347 -
Translational research.....	348 -
12.3. Concluding remarks	350 -
BIBLIOGRAPHY	351 -
Droits d’auteur – Copyright permissions	443 -
Open Access.....	443 -
Permissions for figures.....	444 -
Permissions for published articles	448 -
Institutional repositories.....	450 -
Résumé substantiel en français – Executive summary in French	451 -
Curriculum vitæ.....	457 -
Positions.....	457 -
Diplomas	457 -

Table of contents

Research.....	- 458 -
Responsibilities in scientific societies	- 458 -
Teaching.....	- 459 -
Publications, dissemination and training.....	- 460 -
Publications in journals with peer review.....	- 460 -
Conference papers.....	- 463 -
Oral presentations	- 467 -
Training & transferable skills	- 467 -
Other activities.....	- 468 -
Suppléments – Addenda.....	- 469 -
Addendum 1. Supplementary data for Article 1.....	- 471 -
Addendum 2. Supplementary data for Article 2.....	- 473 -
Addendum 3. Supplementary data for Article 3.....	- 477 -
Addendum 4. Supplementary data for Article 4.....	- 481 -
Addendum 5. Supplementary data for Article 5.....	- 493 -
Addendum 6. Supplementary data for Article 6.....	- 503 -
Addendum 7. Supplementary data for Article 7.....	- 505 -
Addendum 8. Other works associated with the thesis.....	- 509 -
Letter to the editor (E-letter) in the Journal of Clinical Investigation 2018.....	- 509 -
NeuroGASTRO 2019 Abstract #265.....	- 511 -
JFHOD 2020 Abstract #000250	- 515 -
JFHOD 2021 Abstract #000650	- 519 -
neuroGASTRO 2021 Abstract NGS15372-90.....	- 523 -
DDW 2021 Abstract #Sa391.....	- 525 -
Invited review on pyloric distensibility	- 529 -

Sommaire

UEG Week 2022 Abstract #AS-UEG-2022-02097	- 531 -
Index.....	- 535 -



Liste des illustrations – List of figures

FIGURE 1.1. GLOBAL MAPS SHOWING THE COLOUR-CODED WORLDWIDE PREVALENCE OF ANY ROME IV-BASED DISORDER OF GUT-BRAIN INTERACTIONS ACCORDING TO THE ROME FOUNDATION GLOBAL EPIDEMIOLOGY SURVEY.....	- 2 -
FIGURE 1.2. DIAGNOSTIC ALGORITHM HIGHLIGHTING THE RELATIONSHIP BETWEEN DYSPEPSIA, FUNCTIONAL DYSPEPSIA AND H. PYLORI-ASSOCIATED DYSPEPSIA.	- 5 -
FIGURE 1.3. THE SPECTRUM OF FUNCTIONAL SOMATIC SYNDROMES POSSIBLY ASSOCIATED WITH DISORDERS OF GUT-BRAIN INTERACTIONS.	- 34 -
FIGURE 1.4. CONTINUUM BETWEEN OVERACTIVE BLADDER (OAB) AND BLADDER PAIN SYNDROME (BPS).....	- 36 -
FIGURE 1.5. REPRESENTATION OF THE AUTONOMIC INNERVATION OF THE GASTROINTESTINAL TRACT.....	- 50 -
FIGURE 1.6. REPRESENTATION OF THE INNERVATION OF THE GASTROINTESTINAL TRACT.....	- 53 -
FIGURE 1.7. OVERVIEW OF ASCENDING PATHWAYS INVOLVED IN VISCERAL NOCICEPTION FOLLOWING COLORECTAL DISTENSION.	- 56 -
FIGURE 1.8. ONSET OF PAIN AT DIFFERENT VOLUMES OF BALLOON INFLATION IN HEALTHY SUBJECTS VS PATIENTS SUFFERING FROM IRRITABLE BOWEL SYNDROME.....	- 62 -
FIGURE 1.9. ONSET OF ABDOMINAL DISCOMFORT AT DIFFERENT INTRA-GASTRIC PRESSURES IN HEALTHY SUBJECTS VS PATIENTS SUFFERING FROM FUNCTIONAL DYSPEPSIA.	- 63 -
FIGURE 1.10. PUTATIVE MECHANISMS OF CROSS-SENSITISATION BETWEEN THE BLADDER AND THE COLON, DEPICTING THE SUBPOPULATION OF COLON-BLADDER CONVERGENT DRG NEURONS.	- 70 -
FIGURE 1.11. MECHANISTIC MODEL OF CROSS-ORGAN SENSITISATION WITH INTRA-GANGLIONIC CROSSTALK AND SPINAL CENTRAL SENSITISATION.	- 74 -
FIGURE 3.1. PRISMA FLOW DIAGRAM	- 93 -
FIGURE 3.2. FORREST PLOT OF ODDS RATIOS (OR) OF THE PREVALENCES OF IRRITABLE BOWEL SYNDROME IN PATIENTS WITH FUNCTIONAL DYSPEPSIA VS CONTROLS.	- 138 -

Liste des illustrations

FIGURE 4.1. TYPICAL EMPTYING CURVE FOR SOLIDS SHOWING THE TWO PHASES OF GASTRIC EMPTYING.	- 151 -
FIGURE 4.2. CARBON-13-LABELLED OCTANOIC ACID BREATH TESTING.	- 154 -
FIGURE 5.1. CORRELATION BETWEEN THE GLOBAL PSQI AND (A) THE GIQLI AND (B) THE TSS....	- 171 -
FIGURE 6.1. FLOWCHART OF PATIENT SELECTION.	- 189 -
FIGURE 6.2. VENN DIAGRAM SUMMARISING THE FINAL DIAGNOSES IN THE STUDY POPULATION....	- 192 -
FIGURE 7.1. EXAMPLES OF GASTRIC EMPTYING (GE) CURVES USING ¹³ C-LABELLED OCTANOATE BREATH TESTING OVER 480 MINUTES IN PATIENTS WITH SEVERELY DELAYED GE ($T_{1/2} \geq 200$ MINUTES).....	- 206 -
FIGURE 7.2. CORRELATION (A) AND BLAND-ALTMAN PLOT BETWEEN THE CALCULATIONS OF THE GASTRIC HALF-EMPTYING TIME ($T_{1/2}$) OVER 4H AND MORE THAN 6H FOR THE OVERALL POPULATION (B), FOR A $T_{1/2} \leq 200$ MIN (C) AND FOR A $T_{1/2} > 200$ MIN (D).....	- 222 -
FIGURE 7.3. DISTRIBUTION OF THE GASTRIC HALF-EMPTYING TIMES AMONG OUR COHORT, WITH THE PERCENTILE 75 (P75) CORRESPONDING TO 199.5 MINUTES.	- 227 -
FIGURE 8.1. VENN DIAGRAM OF THE STUDY POPULATION.....	- 240 -
FIGURE 8.2. DIFFERENT CHARACTERISTICS OF THE POPULATION ACCORDING TO THE GROUP.....	- 244 -
FIGURE 8.3. COMPARISON OF DYSPEPTIC COMPLAINTS SEVERITY BETWEEN GROUPS.	- 247 -
FIGURE 9.1. MEASUREMENT OF INTRA-COLONIC PRESSURE IN AN AWAKE SPRAGUE-DAWLEY RAT IN A RESTRAINING CAGE.	- 261 -
FIGURE 9.2. BAROSTAT AND THE SYSTEM FOR MEASURING THE PRESSURE IN THE CAROTID ARTERY IN A RAT SEDATED WITH A BARBITURATE.	- 262 -
FIGURE 9.3. THE APICAL JUNCTIONAL COMPLEX.....	- 266 -
FIGURE 10.1. ASSESSMENT OF VISCEROMOTOR RESPONSE TO COLORECTAL DISTENSIONS. .	- 286 -
FIGURE 10.2. BLADDER AND COLORECTAL PERMEABILITIES AND INFLAMMATION.	- 287 -
FIGURE 10.3. QUANTIFICATION OF C-FOS IMMUNOREACTIVE CELLS.....	- 288 -
FIGURE 10.4. NUMBER OF MICROGLIAL CELLS IN THE SPINAL CORD.....	- 290 -

FIGURE 10.5. EFFECT OF MINOCYCLINE INJECTION AT THE CENTRAL LEVEL ON VISCERAL SENSITIVITY.....	- 291 -
FIGURE 10.6. EFFECT OF CP 99994 INJECTION AT THE CENTRAL LEVEL ON VISCERAL SENSITIVITY AND THE EXPRESSION OF PHOSPHORYLATED MAPK-P38.....	- 293 -
FIGURE 10.7. EFFECT OF SB203580 INJECTION AT THE CENTRAL LEVEL ON VISCERAL SENSITIVITY AND THE EXPRESSION OF NK1 RECEPTORS.	- 294 -
FIGURE 10.8. EXPRESSION OF INFLAMMATORY CYTOKINES IN THE SPINAL CORD.	- 296 -
FIGURE 11.1. GASTRIC AND COLONIC INFLAMMATION.....	- 319 -
FIGURE 11.2. OBSERVED CONCENTRATIONS OF PLASMATIC INFLAMMATORY CYTOKINES. ..	- 320 -
FIGURE 11.3. GASTRIC AND COLONIC PERMEABILITIES.	- 321 -
FIGURE 11.4. VISCEROMOTOR RESPONSE TO GASTRIC AND COLORECTAL DISTENSIONS.	- 322 -
FIGURE 11.5. EFFECT OF INTRATHECAL INJECTION OF MINOCYCLINE ON VISCERAL SENSITIVITY.	- 323 -
FIGURE 11.6. EXPRESSION OF PHOSPHORYLATED MAPK-P38.	- 324 -
FIGURE 11.7. EXPRESSION OF PRO-INFLAMMATORY CYTOKINES IN THE SPINAL CORD.	- 325 -
FIGURE 12.1. DIAGRAM OF MOLECULAR AND CELLULAR MECHANISMS UNDERLYING THE DEVELOPMENT OF VISCERAL HYPERSENSITIVITY BY CROSS-SENSITISATION FROM THE BLADDER TO THE COLON.	- 338 -
SUPPLEMENTARY FIGURE 4.1. ANALYSES OF THE GIQLI SCORE.	- 481 -
SUPPLEMENTARY FIGURE 4.2. CORRELATION OF THE GASTROINTESTINAL QUALITY OF LIFE INDEX (GIQLI SCORE) AMONG PATIENTS WITH GASTRIC HALF-EMPTYING TIME ($T_{1/2}$) $\leq$ 200 MIN (A), $T_{1/2}$ $>$ 200 MIN (B) AND COMPARISON OF THE MEAN GIQLI SCORE BETWEEN PATIENTS WITH A $T_{1/2}$ $\leq$ 200 MIN VS $>$ 200 MIN (C) (CALCULATED OVER 6-8 HOURS).	- 482 -
SUPPLEMENTARY FIGURE 4.3. CORRELATION BETWEEN THE GIQLI SCORE AND GASTRIC HALF-EMPTYING TIME.....	- 491 -
SUPPLEMENTARY FIGURE 5.1. PRINCIPAL COMPONENT ANALYSIS (PCA) BIPLLOT OF THE OVERALL DATASET.	- 494 -

Liste des illustrations

SUPPLEMENTARY FIGURE 5.2. PRINCIPAL COMPONENT ANALYSIS (PCA) SCREE PLOT OF THE OVERALL DATASET.....	- 495 -
SUPPLEMENTARY FIGURE 5.3. VENN DIAGRAM SUMMARISING OVERLAP SYNDROMES IN THE ROME III (A) AND ROME IV (B) COHORTS.	- 496 -
SUPPLEMENTARY FIGURE 5.4. DIFFERENT CHARACTERISTICS OF THE ROME III POPULATION ACCORDING TO THE GROUP.	- 497 -
SUPPLEMENTARY FIGURE 5.5. DIFFERENT CHARACTERISTICS OF THE ROME IV POPULATION ACCORDING TO THE GROUP.	- 498 -
SUPPLEMENTARY FIGURE 7.1. EXPRESSION OF NK1R.	- 507 -



Liste des tableaux – List of tables

TABLE 1.1. SUCCESSIVE TERMINOLOGY OF FUNCTIONAL DYSPEPSIA AND ITS SUBGROUPS WITH THEIR SPECIFIC SYMPTOMS.	- 7 -
TABLE 3.1. PREVALENCE OF ORGANIC DISEASES OVERLAPPING WITH FUNCTIONAL DYSPEPSIA.	- 96 -
TABLE 3.2. PREVALENCE OF OTHER DISORDERS OF GUT-BRAIN INTERACTIONS OVERLAPPING WITH FUNCTIONAL DYSPEPSIA.	- 101 -
TABLE 3.3. PREVALENCE OF NON-GASTROINTESTINAL FUNCTIONAL SOMATIC SYNDROMES OVERLAPPING WITH FUNCTIONAL DYSPEPSIA.	- 105 -
TABLE 3.4. PREVALENCE OF PSYCHOLOGICAL FACTORS OVERLAPPING WITH FUNCTIONAL DYSPEPSIA.	- 107 -
TABLE 3.5. PREVALENCES OF DIFFERENT COMORBIDITIES IN FD PATIENTS AND CONTROLS, WITH (POOLED) ODDS RATIOS.	- 112 -
TABLE 4.1. OVERVIEW OF THE SCORES USED IN OUR CLINICAL WORKS.	- 143 -
TABLE 5.1. PATIENT CHARACTERISTICS OF THE OVERALL POPULATION.....	- 167 -
TABLE 5.2. DETAILED CHARACTERISTICS OF SUBJECTIVE SLEEP IN THE OVERALL POPULATION.	- 168 -
TABLE 5.3. COMPARISON OF FD PATIENTS WITH NORMAL VS ALTERED SLEEP QUALITY.	- 169 -
TABLE 5.4. MULTIVARIATE BINARY LOGISTIC REGRESSION MODEL OF FACTORS PREDICTING ALTERED SLEEP QUALITY IN FD PATIENTS.....	- 172 -
TABLE 5.5. MULTIVARIATE BINARY LOGISTIC REGRESSION MODEL OF FACTORS PREDICTING INSOMNIA IN FD PATIENTS.	- 173 -
TABLE 6.1. PATIENT CHARACTERISTICS IN THE OVERALL POPULATION AND ACCORDING TO ROME DIAGNOSES (OUTSIDE ROME, FD ALONE, CNVS ALONE OR FD+CNVS).....	- 194 -
TABLE 6.2. SEVERITY OF DIGESTIVE SYMPTOMS DURING THE PREVIOUS 15 DAYS ACCORDING TO ROME DIAGNOSES (FD ALONE, CNVS ALONE, FD+CNVS OR DYSPEPTIC PATIENTS NOT FULFILLING ROME CRITERIA FOR FD OR CNVS).....	- 197 -

Liste des tableaux

TABLE 6.3. MULTIVARIATE LOGISTIC REGRESSION MODEL OF FACTORS PREDICTING CNVS OVERLAP AMONG ALL FD PATIENTS ACCORDING TO ROME IV CRITERIA.	- 199 -
TABLE 7.1. PATIENT CHARACTERISTICS.	- 215 -
TABLE 7.2. CHARACTERISTICS OF THE POPULATION ACCORDING TO GASTRIC HALF-EMPTYING TIME ($T_{1/2} \leq 166$ MIN OR > 166 MIN (MEASURED OVER 6-8 HOURS)).	- 216 -
TABLE 7.3. SYMPTOMS ACCORDING TO GASTRIC HALF-EMPTYING TIME ($T_{1/2} \leq 166$ MIN OR > 166 MIN (MEASURED OVER 6-8 HOURS)).	- 217 -
TABLE 7.4. CHARACTERISTICS OF THE POPULATION ACCORDING TO GASTRIC HALF-EMPTYING TIME ($T_{1/2} \leq 200$ MIN OR > 200 MIN (MEASURED OVER 6-8 HOURS)).	- 219 -
TABLE 7.5. SYMPTOMS ACCORDING TO GASTRIC HALF-EMPTYING TIME ($T_{1/2} \leq 200$ MIN OR > 200 MIN (MEASURED OVER 6-8 HOURS)).	- 220 -
TABLE 8.1. ESSIC CRITERIA FOR BLADDER PAIN SYNDROME.	- 230 -
TABLE 8.2. PATIENTS' CHARACTERISTICS IN THE OVERALL DYSPEPTIC POPULATION, IN "SYMPTOMATIC CONTROLS", AND IN THE DIFFERENT GROUPS.	- 241 -
TABLE 9.1. OVERVIEW OF AVAILABLE ANIMAL MODELS OF VISCERAL HYPERSENSITIVITY, CLASSIFIED ACCORDING TO THE INSULT'S PERIOD AND TARGET.	- 253 -
TABLE 9.2. OVERVIEW OF AVAILABLE ANIMAL MODELS OF CROSS-ORGAN VISCERAL SENSITISATION INVOLVING THE GUT.	- 258 -
TABLE 11.1. PRIMER SEQUENCES OF GENES OF INTEREST FOR THE RT-qPCR.	- 316 -
TABLE 12.1. SUMMARY OF POTENTIAL PREDISPOSING, PRECIPITATING, PERPETUATING AND PROTECTIVE FACTORS ACROSS BIOPSYCHOSOCIAL DOMAINS IN FUNCTIONAL DYSPEPSIA.	- 343 -
SUPPLEMENTARY TABLE 1.1. GRADES OF RECOMMENDATION, ASSESSMENT, DEVELOPMENT AND EVALUATION APPROACH.	- 471 -
SUPPLEMENTARY TABLE 1.2. DETAILS OF EXTRACTED DATA AMONG ALL ARTICLES INCLUDED IN THE REVIEW.	- 472 -
SUPPLEMENTARY TABLE 2.1. CORRELATIONS BETWEEN THE GLOBAL PSQI AND DIFFERENT QUANTITATIVE PARAMETERS IN OUR POPULATION USING PEARSON CORRELATION COEFFICIENT.	- 473 -

SUPPLEMENTARY TABLE 2.2. COMPARISON OF FD PATIENTS WITH INSOMNIA VS NO INSOMNIA ...	- 474 -
SUPPLEMENTARY TABLE 3.1. COMPARISON OF PATIENTS WITH FD ALONE VS FD+CNVS OVERLAP.	- 478 -
SUPPLEMENTARY TABLE 3.2. MULTIVARIATE LOGISTIC REGRESSION MODEL OF FACTORS PREDICTING CNVS OVERLAP AMONG ALL FD PATIENTS.	- 479 -
SUPPLEMENTARY TABLE 4.1. CHARACTERISTICS OF PATIENTS WITH FUNCTIONAL DYSPEPSIA.....	- 483 -
SUPPLEMENTARY TABLE 4.2. CHARACTERISTICS OF THE POPULATION ACCORDING TO GASTRIC HALF-EMPTYING TIME ($T_{1/2}$) $\leq$ 166 MIN OR $>$ 166 MIN (MEASURED OVER 6-8 HOURS) IN FUNCTIONAL DYSPEPSIA (FD) PATIENTS.	- 484 -
SUPPLEMENTARY TABLE 4.3. SYMPTOMS ACCORDING TO GASTRIC HALF-EMPTYING TIME ($T_{1/2}$) $\leq$ 166 MIN OR $>$ 166 MIN (MEASURED OVER 6-8 HOURS) IN FUNCTIONAL DYSPEPSIA PATIENTS.....	- 485 -
SUPPLEMENTARY TABLE 4.4. UNIVARIATE ANALYSIS OF FACTORS PREDICTING GASTRIC HALF-EMPTYING TIME ($T_{1/2}$) $\leq$ 200 MIN OR $>$ 200 MIN (CALCULATED OVER 8 HOURS).....	- 486 -
SUPPLEMENTARY TABLE 4.5. MULTIVARIATE ANALYSIS OF FACTORS PREDICTING GASTRIC HALF-EMPTYING TIME ($T_{1/2}$) $\leq$ 200 MIN OR $>$ 200 MIN (CALCULATED OVER 8 HOURS).....	- 487 -
SUPPLEMENTARY TABLE 4.6. CHARACTERISTICS OF THE POPULATION ACCORDING TO GASTRIC HALF-EMPTYING TIME ($T_{1/2}$) $\leq$ 200 MIN OR $>$ 200 MIN (MEASURED OVER 6-8 HOURS) IN FUNCTIONAL DYSPEPSIA (FD) PATIENTS.	- 488 -
SUPPLEMENTARY TABLE 4.7. SYMPTOMS ACCORDING TO GASTRIC HALF-EMPTYING TIME ($T_{1/2}$) $\leq$ 200 MIN OR $>$ 200 MIN (MEASURED OVER 6-8 HOURS) IN FUNCTIONAL DYSPEPSIA PATIENTS.....	- 489 -
SUPPLEMENTARY TABLE 4.8. SYMPTOMS ACCORDING TO GASTRIC HALF-EMPTYING TIME ($T_{1/2}$) $\leq$ 200 MIN OR $>$ 200 MIN (CALCULATED OVER 4 HOURS).....	- 490 -

Liste des tableaux

SUPPLEMENTARY TABLE 5.1. 8-ITEM SYMPTOM-BASED SELF-QUESTIONNAIRE BASED ON THE ESSIC CRITERIA PUBLISHED IN 2008 FOR THE DIAGNOSIS OF BLADDER PAIN SYNDROME.	- 499 -
SUPPLEMENTARY TABLE 5.2. MAIN DATA OF EACH ACTIVE VARIABLE USED IN THE PRINCIPAL COMPONENT ANALYSIS (PCA).....	- 500 -
SUPPLEMENTARY TABLE 5.3. MULTIVARIATE LINEAR REGRESSION MODEL WITH BPS AS THE DEPENDENT VARIABLE.....	- 501 -
SUPPLEMENTARY TABLE 6.1. PRIMER SEQUENCES FOR THE TARGETED MOUSE GENES FOR POLYMERASE CHAIN REACTION.....	- 503 -
SUPPLEMENTARY TABLE 7.1. CHARACTERISTICS OF ANIMALS FROM THE FIRST SERIES ACCORDING TO THE THREE GROUPS (SALINE, TNBS AT DAY 2 AND TNBS AT DAY 7).	- 505 -



Glossaire – Abbreviations & acronyms

Δ	variation
$^{13}\text{CO}_2$	carbon-13 labeled CO_2
3Rs	the “Three Rs” (Replacement, Reduction and Refinement)
5-HT	serotonin
5-HT ₃	5-hydroxytryptamine 3 (receptor)
5-HTTLPR	serotonin-transporter-linked promoter region
α -MSH	alpha-MSH
<i>A. muciniphila</i>	<i>Akkermancia muciniphila</i>
AA	acetic acid
ACC	anterior cingulate cortex
ADHD	attention deficit hyperactivity disorder
ADP	adenosine diphosphate
Akt	protein kinase B
a.m.	ante meridiem
AMP	adenosine monophosphate
ANOVA	analysis of variance
ANS	autonomic nervous system
ARFID	avoidant/restrictive food intake disorder
ATM	axon tract-associated microglia
ATP	adenosine triphosphate
AU	arbitrary unit(s)
AUC / A.U.C.	area under the curve
AWR	abdominal withdrawal reflex
B	unstandardised regression coefficient
BCA	bicinchoninic acid
BDNF	brain-derived neurotrophic factor
BMI	body mass index
BPS	bladder pain syndrome
BREESI	Brief Environmental Exposure and Sensitivity Inventory
BSA	bovine serum albumin
CA	California (state)
cAMP	cyclic adenosine monophosphate

Glossaire

CaV	voltage-gated calcium channels
CD	cluster of differentiation
cDNA	complementary DNA
CED	Cambridge Electronic Design
CEP	cerebral evoked potentials
CERNI	comité d'éthique pour la recherche non-interventionnelle
CESAM	Centre d'Enseignement de la Statistique à la Santé Publique, à la Médecine et à la Biologie
CFS	chronic fatigue syndrome
CG	coeliac ganglion
CGRP	calcitonin gene-related peptide
CH ₄	methane
ChAT	choline acetyltransferase
CHS	cannabinoid hyperemesis syndrome
CI	confidence interval
CIC-CRB	Centre d'investigation clinique-Centre de Ressources Biologiques
CNIL	Commission Nationale de l'Informatique et des Libertés
CNS	central nervous system
CNV	chronic nausea and vomiting
CNVS	chronic nausea and vomiting syndrome
CO	Colorado (state)
CO ₂	carbon dioxide
COVID-19	coronavirus disease 2019
COX-2	cyclooxygenase-2
CPP	Comité de Protection des Personnes
CPPS	chronic pelvic pain syndrome
CRD	colorectal distension(s)
CREB	cAMP response element-binding protein (transcription factor)
CSF	cerebrospinal fluid
CSF-1	colony-stimulating factor-1
CSF-1R	colony-stimulating factor-1 receptor
CSI	comité de suivi individuel
CSM	circular smooth muscle
Ct	cycle threshold
CUSL	Cliniques universitaires Saint-Luc

CVS	cyclic vomiting syndrome
CX3CL1	fractalkine
CX3CR1	fractalkine receptor, or CX3C motif chemokine receptor 1
d	days
D1	day 1
D2	day 2
D7	day 7
Da	daltons
DALY	disability-adjusted life years
DAM	disease-associated microglia
DAO	diamine oxidase
DAPI	4',6-diamidino-2-phenylindole
DCML	dorsal column-medial lemniscus pathway
DDW	Digestive Disease Week
DGBI	disorders of gut-brain interactions
DNA	deoxyribonucleic acid
DOI	Digital Object Identifier
DRG	dorsal root ganglion/ganglia
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5 th edition
DSS	dextran sodium sulphate
DSSI	Dyspepsia Symptom Severity Index
DTPA	diethylenetriamine pentaacetate
E-cadherin	epithelium cadherin
ECG	electrocardiogram
<i>E. coli</i>	<i>Escherichia coli</i>
EDS	Ehlers-Danlos syndrome(s)
EDTA	ethylenediaminetetraacetic acid
EEG	electroencephalogram
EGG	electrogastrography
EGIDs	eosinophilic gastrointestinal disorders
ELISA	enzyme-linked immunosorbent assay
EMG	electromyography
ENS	enteric nervous system
EoE	eosinophilic oesophagitis
EPAN	extrinsic primary afferent neuron(s)

Glossaire

EPS	epigastric pain syndrome
EQ-5D	EuroQol-5 dimension
ERK	extracellular signal-regulated kinase
ESSIC	European Society for the Study of Interstitial Cystitis
EUS	endoscopic ultrasound
FD	functional dyspepsia
FELASA	Federation of European Laboratory Animal Science Associations
FGIDs	functional gastrointestinal disorders
FIRST	fibromyalgia rapid screening tool
FITC	fluorescein isothiocyanate
FKN	fractalkine
fMRI	functional magnetic resonance imaging
FODMAP	fermentable oligosaccharides, disaccharides, monosaccharides, and polyols
g	g-force (or relative centrifugal force, RCF) grams
GABA	gamma-aminobutyric acid
GAD-7	Generalised Anxiety Disorder 7-item (scale)
GALT	gut-associated lymphoid tissue
GAPDH	glyceraldehyde 3-phosphate dehydrogenase
GATHER	guidelines for accurate and transparent health estimates reporting
GNDF	glial cell-derived neurotrophic factor
GDPR	general data protection regulation
GDSS	Glasgow Dyspepsia Severity Score
GE	gastric emptying
GEC	gastric emptying coefficient
GFP	green fluorescent protein
GI	gastrointestinal
GIQLI	GastroIntestinal Quality of Life Index
GJ	gap junction (proteins)
GNB3	G-protein $\beta 3$
GOR	gastro-oesophageal reflux
GORD	gastro-oesophageal reflux disease
G-POEM	gastric per-oral endoscopic myotomy
GPR15	G protein-coupled receptor 15

GRADE	grades of recommendation, assessment, development and evaluation
GSH-R	growth hormone secretagogue receptor (or ghrelin receptor)
GSRS	Gastrointestinal Symptom Rating Scale
H ₂	hydrogen
h ²	narrow-sense heritability
h _{SNP}	SNP heritability
h ² _{SNP}	narrow-sense and common SNP heritability
H ₂ O	water
H ₂ ¹⁵ O	oxygen-15-labeled water
H ₂ O ₂	hydrogen peroxide
H+1	one hour after intracolonic administration
HαT	hereditary alpha tryptasemia
HAD	hospital anxiety and depression
HADS	HAD scale
HADS-A	HADS anxiety subscale
HADS-D	HADS depression subscale
HBSS	Hank's Balanced Salt Solution
HCl	hydrochloric acid
hEDS	hypermobile EDS
HF	high-frequency (band of heart rate oscillations)
HH	hiatal hernia
HPA	hypothalamic-pituitary-adrenal (axis)
<i>H. pylori</i>	<i>Helicobacter pylori</i>
HR-QoL	health-related QoL
HRV	heart rate variability
HTAB	hexadecyltrimethylammonium bromide
HTF	high-throughput fluidics
Hz	hertz (one cycle per second)
IASP	International Association for the Study of Pain
Iba1	ionised calcium-binding adaptor molecule-1
IBD	inflammatory bowel disease(s)
IBS	irritable bowel syndrome
IC/BPS	interstitial cystitis/bladder pain syndrome
IC/PBS	interstitial cystitis/painful bladder syndrome

Glossaire

ICD	International Classification of Diseases
ICD-10	ICD, 10 th revision
ICD-10-CM	ICD-10 with clinical modification
ICD-11	ICD, 11 th revision
ICHD-II	international classification of headache disorders 2 nd edition
ICHD-3	international classification of headache disorders 3 rd edition
ICP	intracolonic pressure
ICV	intracerebroventricular
I-FABP	intestinal fatty acid binding protein
IFAN	intestino-fugal primary afferent neuron(s)
IgE	immunoglobulin E
IGP	intra-gastric pressure
IHS	International Headache Society
IL	interleukin Illinois (state, when preceding "USA")
IL-1 β	interleukin-1 beta
IMG	inferior mesenteric ganglion
iNOS	inducible nitric oxide synthase
INSERM	Institut national de la santé et de la recherche médicale
IPAN	intrinsic primary afferent neuron(s)
IR	immunoreactive
IREC	Institut de Recherche Expérimentale et Clinique
IRIB	Institut de Recherche et d'Innovation Biomédicale
IRIS	InfraRed ISotope (analyser)
ISI	insomnia severity index
IT	intrathecal
IV	intravesical
JFHOD	Journées Francophones d'Hépatogastroentérologie et d'Oncologie Digestive
JHS	joint hypermobility syndrome
kDa	kilodaltons
kJ	kilojoules
KV	voltage-gated potassium channels
LBP	LPS binding protein
LCT	lactase (gene)

Abbreviations

LDAM	lipid-droplet-accumulating microglia
LDQ	Leeds Dyspepsia Questionnaire
LF	low-frequency (band of heart rate oscillations)
LMR	lactulose:mannitol ratio
LPDS	Leuven Postprandial Distress Scale
LPS	lipopolysaccharide
LSM	longitudinal smooth muscle
M	molar (mol/L)
MA	Commonwealth of Massachusetts (state)
MadCAM-1	mucosal vascular addressin cell adhesion molecule-1
MAL	myelin and lymphocyte
MAPK	mitogen-activated protein kinase
MARVEL	MAL and related proteins for vesicle trafficking and membrane link (domain)
MCAS	mast cell activation syndrome
MCC	midcingulate cortex
ME	myalgic encephalomyelitis
MEG	magnetoencephalography
MII-pH	multichannel intraluminal impedance-pH testing
MRGPRX2	Mas-related G protein-coupled receptor X2
M-MLV	Moloney Murine Leukemia Virus
MN	Minnesota
MO	Missouri
MP	myenteric plexus
mPET	micro-PET
MPO	myeloperoxidase
MRI	magnetic resonance imaging
mRNA	messenger RNA
MScCT	Master of Science in Clinical Trials
MSH	melanocyte-stimulating hormone
mTOR	mammalian target of rapamycin
MW	molecular weight
n	number
n.	nerve
NaCl	saline

Glossaire

NaV	voltage-gated sodium channels
NCGS	non-coeliac gluten/wheat sensitivity
NDI	Nepean Dyspepsia Index
NERD	non-erosive reflux disease
NFκB	nuclear factor-κB
NG	nodose ganglion/ganglia
NGF	nerve growth factor
NJ	New Jersey (state)
NK	natural killer (cells)
NK1	neurokinin-1 or substance P
NK1R	neurokinin-1 receptor
NMDA	N-methyl-D-aspartate
NNT	number needed to treat
NO	nitric oxide
NOS	nitric oxide synthase
NPY	neuropeptide Y
ns	non-significant
NSAID	nonsteroidal anti-inflammatory drugs
NTS	nucleus tractus solitarii (or nucleus of the solitary tract)
NUD	non-ulcer dyspepsia
OAB	overactive bladder
OCT	optimal cutting temperature
ODHC	O-dianisidine dihydrochloride
OGD	oesophagogastrroduodenoscopy
OGJOO	oesophagogastric junction outflow obstruction
ON	Ontario (state)
OR	odds ratio Oregon (state, when preceding "USA") or (boolean operator, in the Search strategy of Chapter 3)
p	p-value(s)
P2X	purinergic (receptors)
P2Y	purinergic (receptors)
pACC	perigenual anterior cingulate cortex
PAGI-QOL	patient assessment of upper gastrointestinal disorders-quality of life

PBS	phosphate-buffered saline
PC	principal component
PCA	principal component analysis
PCR	polymerase chain reaction
PDS	postprandial distress syndrome
PEG	polyethylene glycol
PET	positron emission tomography
PGE2	prostaglandin E2
PHQ-9	Patient Health Questionnaire-9 items
PHQ-12	Patient Health Questionnaire-12 items
PHQ-15	Patient Health Questionnaire-15 items
PI	post-infectious
PI3K	phosphatidylinositol 3-kinases
PLA2	phospholipase A2
p.m.	post meridiem
PNNL	Pacific Northwest National Laboratory
POTS	postural orthostatic tachycardia syndrome
P-p38	phosphorylated MAPK-p38
PPI	proton pump inhibitor(s)
PRC	Popular Republic of China
PRISMA	preferred reporting items for systematic reviews and meta-analyses
PRO	patient-reported outcome(s)
PROMIS	Patient-Reported Outcomes Measurement Information System
PROMs	patient-reported outcome measures
PRS	partial restraint stress
PSQI	Pittsburgh sleep quality index
PTSD	post-traumatic stress disorder
QEESI®	Quick Environmental Exposure and Sensitivity Inventory
QoL	quality of life
QOLRAD	Quality of Life in Reflux and Dyspepsia questionnaire
qPCR	quantitative polymerase chain reaction
R3DQ	Rome III diagnostic questionnaire (for FGIDs in adults)
R4DQ	Rome IV diagnostic questionnaire (for FGIDs in adults)
RALDH	retinaldehyde dehydrogenase

Glossaire

rCBF	regional cerebral blood flow
RCT	randomised controlled trial
Refs	references
RIII	nociceptive flexor reflex
RNA	ribonucleic acid
ROUT	robust regression and outlier removal
rpm	revolutions per minute
RPS18	ribosomal protein S18
RT-qPCR	reverse transcription-quantitative PCR
RVM	rostral ventromedial medulla
SAN	secondary afferent neuron
SARS-CoV	severe acute respiratory syndrome coronavirus
SD	standard deviation
SE	standard error
SEM	standard error of the mean
SF-12	medical outcome study - short form 12 items (score)
SF-36	medical outcome study - short form 36 items (score)
SF-NDI	short form Nepean dyspepsia index
SGCs	satellite glial cells
SI	primary somatosensory cortex
SIBO	small intestinal bacterial overgrowth
slgA	secretory immunoglobulin A
SII	secondary somatosensory cortex syndrome de l'intestin irritable (IBS in French)
SLE	systemic lupus erythematosus
SMG	superior mesenteric ganglion
SMP	submucosal plexus
<i>S. muris</i>	<i>Syphacia muris</i>
SNP	single nucleotide polymorphism
SOD	sphincter of Oddi dysfunction
SODA	Severity of Dyspepsia Assessment
SP	substance P
SPECT	single-photon emission computed tomography
spp.	<i>species pluralis</i>
SQ	starting quantities

sqRT-PCR	semi-quantitative RT-PCR
SSS	Secteur des Sciences de la Santé
SSS-8	Somatic Symptom Scale-8
SUDD	symptomatic uncomplicated diverticular disease
SyGAL	Système de Gestion et d'Accompagnement doctoral
T½	gastric half-emptying time
TAC1	Tachykinin Precursor 1 (gene)
TAMPs	tight junction-associated MARVEL proteins
TARGID	Translational Research Center for Gastrointestinal Disorders
ta-VNS	transcutaneous auricular vagal nerve stimulation
TBS	Tris-buffered saline
TBS-T	Tris-buffered saline containing Tween® 20
TEER	transepithelial electrical resistance
TLESRs	transient lower oesophageal sphincter relaxations
Tm	melting temperature
TMEM119	transmembrane protein 119
TNBS	2,4,6-trinitrobenzene sulphonic acid (or picrylsulfonic acid)
TNF-α	tumour necrosis factor-alpha
TrkA	tropomyosin receptor kinase A
TRPA1	transient receptor potential ankyrin 1
TRPV	transient receptor potential vanilloid
TRPV1	transient receptor potential vanilloid 1
TSS	total symptom score
TX	Texas (state)
U	unit
UC	ulcerative colitis
UCL	Université catholique de Louvain (UCLouvain)
UEG	United European Gastroenterology
UK	United Kingdom
ULF	ultra-low-frequency (band of heart rate oscillations)
US	United States
USA	United States of America
VAS	visual analogue scale
VIF	variance inflation factor
VIP	vasoactive intestinal peptide

Glossaire

VLF	very-low-frequency (band of heart rate oscillations)
VMR	visceromotor response(s)
VPI	ventral posterior inferior nucleus of the thalamus
VPL	ventral posterior lateral nucleus of the thalamus
VS	Visceral Sensitivity Index
WA	Washington (state)
WAM	white matter-associated microglia
WAS	water avoidance stress
WB	western blot
WHO	World Health Organisation
WHS	Women Health Study
WKY	Wistar Kyoto rat strain
w/v%	weight/volume percentage (= g of solute /100mL of solution)
ZO	zonula occludens (protein)



Chapter 1 INTRODUCTION

1.1. Disorders of gut-brain interactions: focus on functional dyspepsia

DISORDERS OF GUT-BRAIN INTERACTIONS (DGBI), previously called “functional gastrointestinal (GI) disorders” (FGIDs), are a significant public health problem, consuming healthcare resources (Sabaté et al., 2019), with an estimated prevalence in Western countries of approximately 40% (Sperber et al., 2021), as shown in Figure 1.1. They are defined by symptoms evocative of a digestive origin without underlying organic disease. The field of study of these diseases is called neurogastroenterology and is still under-taught in medical education (Simons et al., 2022). Symptom generation is thought to arise from a mix of different pathogenic mechanisms, such as variations in gut microbiota, mucosal immune activation, visceral hypersensitivity and the impaired integration of gut signals by the central nervous system (CNS). The **gut-brain axis** refers to the bidirectional communications between the GI tract and the CNS. Dysregulation of the signalling between the enteric nervous system (ENS) and the CNS is central in their pathophysiology, explaining their generic name.

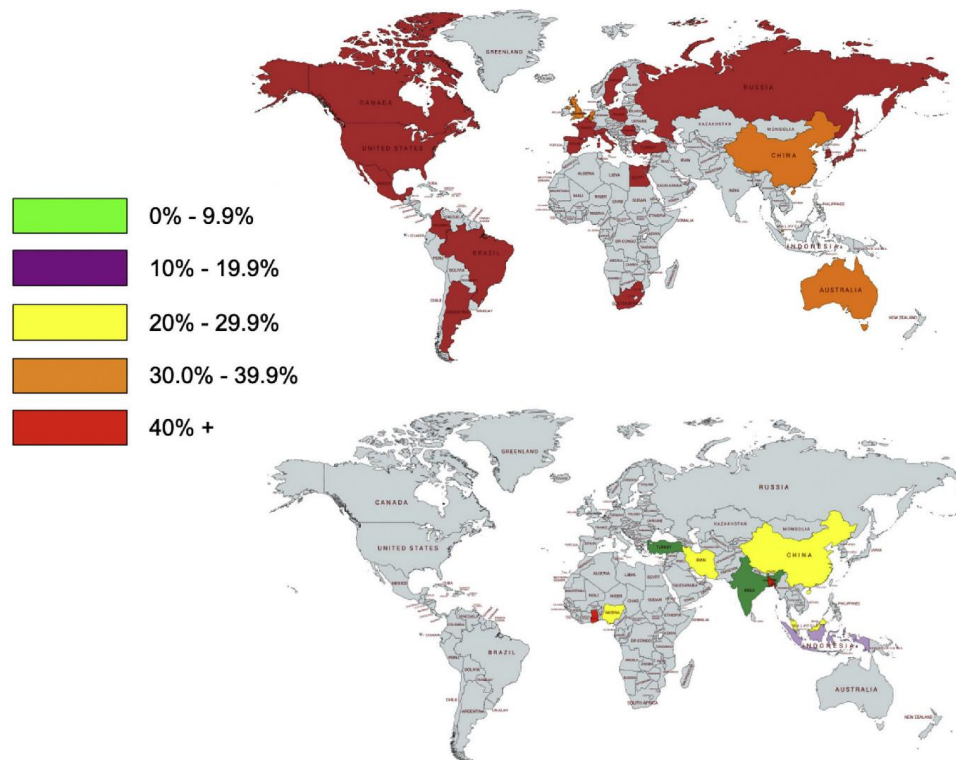


Figure 1.1. Global maps showing the colour-coded worldwide prevalence of any Rome IV-based disorder of gut-brain interactions according to the Rome Foundation Global Epidemiology Survey.

Different maps according to the data collection method: internet above, household interviews below.

Reproduced from Sperber et al. (Sperber et al., 2021). © 2021 by the AGA Institute. Published by Elsevier Inc.

Definitions

Dyspepsia (from the Greek *dyspeptos* meaning "bad digestion") is the medical term for *indigestion*, which relates to complaints of discomfort in the upper abdomen. Human beings have always been annoyed by dyspeptic symptoms, with known references to the term in the writings of Hippocrates and Galen 2,000 years ago. Symptoms of dyspepsia can be acute (after acute gastroenteritis, for example) or chronic. Dyspepsia is a group of symptoms and

not a disease. It is defined by four cardinal symptoms (postprandial fullness, early satiation, epigastric pain and non-radiating epigastric burning). Still, other symptoms also belong to the dyspeptic spectrum, such as nausea, belching and upper abdominal bloating. Conversely, heartburn is no longer considered a dyspeptic symptom even if it frequently coexists with dyspepsia, and vomiting is regarded as an alarm symptom for an underlying organic disease.

When those symptoms do occur, the condition is called **uninvestigated dyspepsia** before testing for underlying causes. Patients with dyspeptic symptoms may indeed have structural, metabolic or systemic diseases explaining their symptoms, which mainly include peptic ulcer disease, gastro-oesophageal reflux disease (GORD) with reflux oesophagitis, gastric or oesophageal carcinomas, adverse drug reactions (nonsteroidal anti-inflammatory drugs (NSAID), metformin, iron, opioids, etc.), metabolic disturbances (hypercalcemia, hyperkalaemia), systemic disorders (diabetic gastroenteropathy, systemic sclerosis, etc.), pancreatic or biliary diseases, and so on. These patients are finally diagnosed with **organic dyspepsia** or **secondary dyspepsia**. The workup of patients with dyspeptic complaints remains normal in most cases, with a final diagnosis of **idiopathic dyspepsia**. Idiopathic dyspepsia has previously been referred to as **non-ulcer dyspepsia** or **essential dyspepsia**, but the preferred term nowadays is **functional dyspepsia** (FD). The workup can, however, be limited to an upper GI endoscopy in clinical routine in most patients. The most common endoscopic findings in patients with uninvestigated dyspepsia are erosive oesophagitis and peptic ulcers, with prevalences of 13.4% and 8.0%, respectively, in a meta-analysis of Western studies (Ford et al., 2010b). In this work, 67.2% of patients with **investigated dyspepsia** were found to have FD. *Helicobacter pylori* gastritis is now considered a distinct cause of dyspepsia, and ***H. pylori*-associated dyspepsia** as a separate entity, since the Kyoto consensus (Sugano et al., 2015). Indeed, *H. pylori* eradication has been shown to induce sustained symptom improvement in some patients (Malfertheiner et al., 2003). Eradication is always indicated if *H. pylori* is present due to the improvement of symptoms after eradication when compared with placebo (the relative risk of remaining dyspeptic is 0.91 (95% confidence interval [CI]: 0.89-0.94), with a number needed to treat (NNT) of 14 (95% CI: 11-21) (Ford et al., 2022). Additional benefits of this eradication are preventing peptic ulcers (Jiang et al., 2021) and possibly gastric carcinoma and lymphoma in these patients (Chiang et al., 2021). A diagnosis of FD

in patients with *H. pylori*-positive gastritis and dyspeptic complaints is therefore only possible 6 to 12 months after *H. pylori* eradication in cases of persistent symptoms. The relationship between dyspepsia, FD and *H. pylori*-associated dyspepsia is depicted in Figure 1.2. Furthermore, the final diagnosis of FD may or may not meet the Rome criteria. Functional dyspepsia is currently defined in a research setting by the Rome criteria, with the most recent version being Rome IV (Stanghellini et al., 2016). Patients must have at least one of the four cardinal dyspeptic symptoms described above, no evidence of organic disease that is likely to explain their complaints (especially at upper GI endoscopy), chronic (symptom onset at least six months before diagnosis) and active (criteria must be fulfilled for the last three months) disorder to meet these criteria (Stanghellini et al., 2016). Based on meal-related or meal-unrelated complaints, two subgroups of FD patients can be identified: **postprandial distress syndrome** (PDS) and **epigastric pain syndrome** (EPS), which can coexist in a single patient. The Rome criteria for one or both subtypes must be met to satisfy the Rome definition of the disorder (Stanghellini et al., 2016).

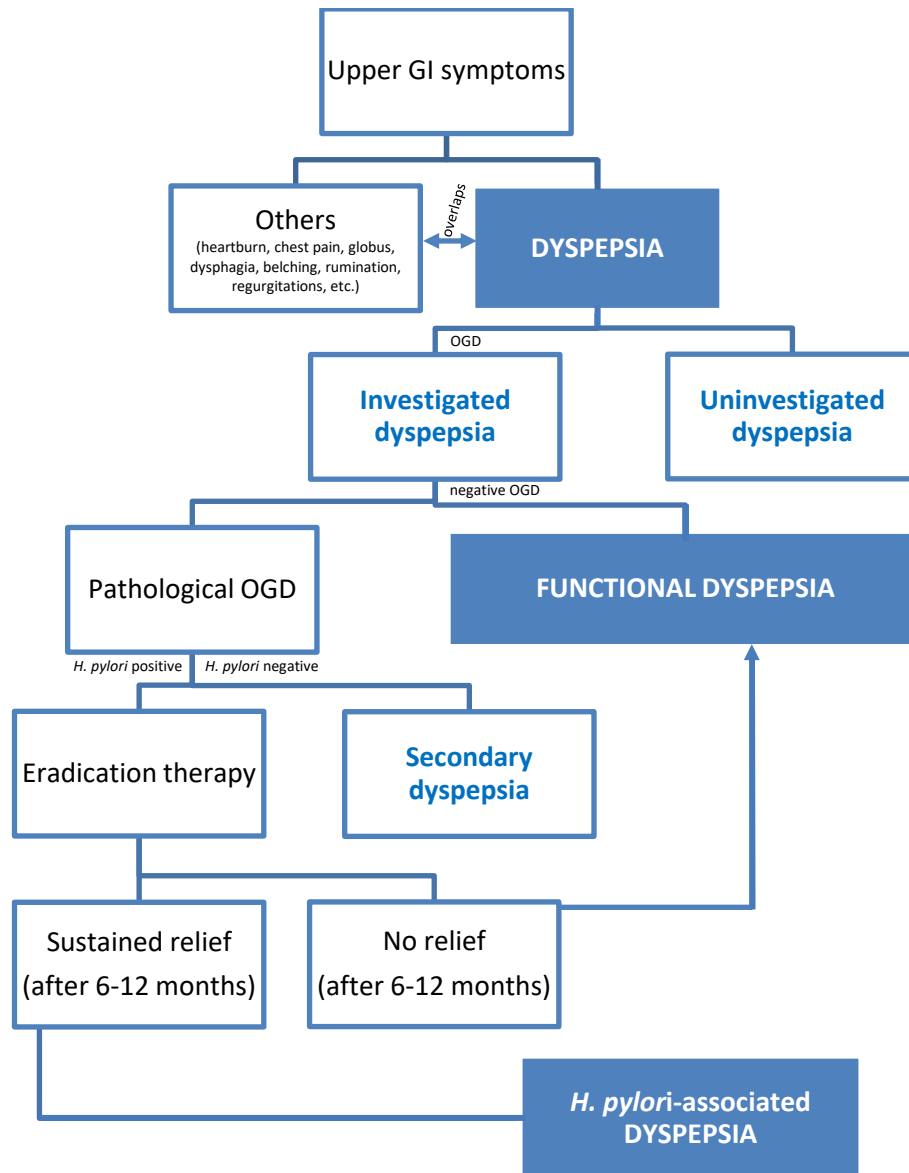


Figure 1.2. Diagnostic algorithm highlighting the relationship between dyspepsia, functional dyspepsia and *H. pylori*-associated dyspepsia.

OGD: oesophagogastroduodenoscopy, GI: gastrointestinal, *H. pylori*: *Helicobacter pylori*.

Adapted from Talley et al. (Talley et al., 1999b) and Sugano et al. (Sugano et al., 2015).

The **Rome criteria** for the diagnosis of FD have evolved, as summarised in Table 1.1, except for the need to exclude organic diseases at the origin of the symptoms. **Rome I** defined FD as chronic or recurrent pain or discomfort centred in the upper abdomen, which had to be present at least one day per week for the last three months, and differentiated three subgroups: ulcer-like, dysmotility-like and reflux-like dyspepsia (Talley et al., 1991, Drossman et al., 1994). At that time, heartburn was not an exclusion criterion, and vomiting was part of the dysmotility-like symptoms. **Rome II** defined FD as persistent or recurrent pain or discomfort centred in the upper abdomen during at least 12 (not necessarily consecutive) weeks within the last 12 months and differentiated three subgroups: ulcer-like (predominant pain), dysmotility-like (predominant non-painful symptom) and unspecified dyspepsia (Talley et al., 1999b, Drossman et al., 2000). Patients with predominant heartburn were excluded from the FD spectrum. However, overlap syndromes with irritable bowel syndrome (IBS) and non-predominant heartburn were recognised. Vomiting was considered an alarm symptom in this iteration of Rome criteria. **Rome III** defined FD at two levels: an “umbrella” definition to be used in clinical practice, and subgroups for research purposes (Tack et al., 2006, Drossman et al., 2006). Patients needed to have at least one of the four cardinal symptoms (bothersome postprandial fullness, early satiation, epigastric pain and epigastric burning), with symptom onset at least six months before and criteria being fulfilled for the last three months. A diagnosis of EPS required intermittent pain or burning specifically at the epigastrium, not related to defecation, without criteria for gallbladder or sphincter of Oddi disorders, and occurring at least once per week. **Rome IV** criteria (Stanghellini et al., 2016, Drossman et al., 2016) were only slightly changed compared to Rome III: all symptoms now need to be severe enough to affect usual activities (and not only postprandial fullness), postprandially-occurring symptoms, as nausea, belching and epigastric pain, are now part of the PDS spectrum, PDS symptoms have to be present at least three days per week (and not "at least several times per week"), persistent vomiting suggests another disorder, and epigastric pain in EPS is not required to be intermittent anymore.

Table 1.1. Successive terminology of functional dyspepsia and its subgroups with their specific symptoms.

Criteria (year)	Terminology	Subgroups	Specific symptoms
Before Rome	Non-ulcer dyspepsia (NUD), etc.	/	/
Rome I (1994)	Functional dyspepsia (FD)	ulcer-like dyspepsia	pain centred in the upper abdomen
		dysmotility-like dyspepsia	discomfort centred in the upper abdomen (early satiation, postprandial fullness, bloating, nausea, retching, vomiting)
		reflux-like dyspepsia	heartburn regurgitation
Rome II (1999)	Functional dyspepsia (FD)	ulcer-like dyspepsia	pain centred in the upper abdomen
		dysmotility-like dyspepsia	discomfort centred in the upper abdomen (upper abdominal fullness, early satiety, bloating, or nausea)
		unspecified (non-specific) dyspepsia	symptoms not fulfilling the criteria for ulcer-like or dysmotility-like dyspepsia
Rome III (2006)	Functional dyspepsia (FD)	epigastric pain syndrome (EPS)	epigastric pain epigastric burning
		postprandial distress syndrome (PDS)	early satiation postprandial fullness
Rome IV (2016)	Functional dyspepsia (FD)	epigastric pain syndrome (EPS)	epigastric pain epigastric burning
		postprandial distress syndrome (PDS)	early satiation postprandial fullness

The diagnosis of FD is coded DD90.3 in the International Classification of Diseases, 11th revision (ICD-11 of the World Health Organisation, WHO) and K30 in its latest US iteration with clinical modification (ICD-10-CM). The EPS subtype is also coded elsewhere as "chronic primary epigastric pain syndrome" (MG30.00) in ICD-11.

Epidemiology

Uninvestigated dyspepsia has an overall **prevalence** of 20.8% (95% CI: 17.8-23.9) (Ford et al., 2015). Its prevalence varies among countries, which suggests that there are environmental, cultural, ethnic, dietary or genetic influences. Its prevalence also varies according to the criteria used for the diagnosis: the prevalence decreases with each successive iteration of the Rome criteria, from 17.6% (95% CI: 9.8-27.1) using the Rome I criteria to 6.9% (95% CI: 5.7-8.2) using the Rome IV criteria (Barberio et al., 2020).

The worldwide prevalence rate of FD, according to Rome IV criteria, is 7.2% (95% CI: 7.1-7.4) according to an internet survey (Western world) and 4.8% (95% CI: 4.5-5.1) according to a household survey (developing countries) (Sperber et al., 2021). Its prevalence rate is 5.0% (95% CI: 4.0-5.9) in Belgium and 8.5% (95% CI: 7.3-9.7) in France. There are wide disparities across countries: 0.7% (95% CI: 0.5-1.0) in India, 2.4% (95% CI: 1.8-3.0) in Japan, 12.3% (95% CI: 10.8-13.7) in Egypt and 19.4% (95% CI: 17.7-21.2) in Bangladesh for instance (Sperber et al., 2021).

Functional dyspepsia is the most common and the prototype of **functional gastro-duodenal disorders**, which also include excessive gastric/supragastric belching, chronic nausea and vomiting syndrome (CNVS), cyclic vomiting syndrome (CVS), cannabinoid hyperemesis syndrome (CHS) and rumination syndrome. It is also one of the most common DGBI. Indeed, in Belgium, the prevalences of IBS, functional constipation, functional diarrhoea and functional abdominal bloating are 3.3% (95% CI: 2.5-4.0), 11.0% (95% CI: 9.7-12.4), 4.0% (95% CI: 3.2-4.9) and 2.4% (95% CI: 1.7-3.0) respectively (Sperber et al., 2021).

Postprandial distress syndrome is more frequent than EPS among subtypes, with a distribution of about two-thirds of PDS, 15-20% of EPS and 15-20% of PDS-EPS overlap (Aziz et al., 2018a).

The prevalence of FD decreases with age across the adult lifespan and is most common among young adults (Sperber et al., 2021). Female predominance is found in all western studies, with about 1.5 women suffering from the disorder for every man (Sperber et al., 2021), as is the case with IBS. Functional dyspepsia is associated with body mass index (BMI) in women, forming a U-shaped relationship (higher odds for the disorder in underweight and obesity subgroups) (Le Pluart et al., 2015).

Risk factors for uninvestigated dyspepsia are NSAID use (Shaib and El-Serag, 2004), female gender (Talley et al., 1994), *H. pylori* infection, young age and smoking (Olafsdottir et al., 2012, Ford et al., 2015). Smoking is a risk factor for the PDS subtype (Talley et al., 2021). Conversely, the most documented risk factors for FD include previous history of acute gastroenteritis, unemployment, divorce, smoking, IBS comorbidity, anxiety and coronavirus disease 2019 (COVID-19). Indeed, infections by norovirus, *Giardia lamblia*, *Salmonella spp.*, *Escherichia coli* O157 and *Campylobacter spp.* are associated with the occurrence of post-infectious FD (PI-FD), but not *H. pylori* (Futagami et al., 2015). An Italian general population-based endoscopic study found that smoking, divorce, unemployment, and having concurrent IBS were risk factors for FD (Zagari et al., 2010). Anxiety increased the risk of developing FD by 7.6 times in the next ten years in the Kalixanda study, a population-based follow-up study in Sweden (Aro et al., 2015), but not depression (Aro et al., 2009). More recently, increased risk of FD was found in people who survived COVID-19 (OR 1.36 [95% CI: 1.22-1.51]) (Xu et al., 2023).

Pathophysiology

Functional dyspepsia is a complex disorder with multiples pathways involved in its pathophysiology: gastric inflammation (history of *H. pylori* gastritis, etc.), visceral hypersensitivity (to acid, gastric wall distension, etc.), duodenal inflammation (role of acid, bacteria, viruses, bile, local immune activation, etc.), dysbiosis, decreased fundic accommodation, abnormal distribution of gastric contents, delayed gastric emptying (GE), abnormal myoelectrical activity, intestinal dysmotility, altered CNS modulation (anxiety, stress, etc.), and so on (Stanghellini et al., 2016).

Genetics play only a minor role in the pathogenesis of FD, with a heritable component estimated at 5% ($h_{SNP}^2 = 0.047$, $p = 0.014$) based on data from three large population-based biobanks (Garcia-Etxebarria et al., 2022). In this study, 13 loci were associated with a risk of FD, with two (tagged by markers rs2093045 on chromosome 20 and rs2189730 on chromosome 9) replicated in an independent cohort. Patients with homozygous carrier status for the G-protein $\beta 3$ (*GNB3*) subunit gene polymorphism (C825T) are at higher risk of developing FD (Holtmann et al., 2004). Concordantly, a twin study showed no genetic contribution to upper abdominal pain, unlike IBS and GORD (Lembo et al., 2007).

A few years ago, experts in the field emphasised impaired accommodation and delayed GE as the most plausible pathophysiological mechanisms implicated in symptom generation in the disorder (Tack et al., 2018). The underlying hypothesis is that alterations of GI sensorimotor functions underlie the occurrence of symptoms in FD. The prevalences of gastric hypersensitivity, impaired fundic accommodation, and delayed GE were 37%, 37% and 23%, respectively, in FD patients in a tertiary care centre (Vanheel et al., 2017). Classifying patients in EPS and PDS subtypes according to the predominant symptom of the patients does not predict underlying pathophysiological mechanisms (Karamanolis et al., 2006).

Fundic accommodation is the relaxation of the proximal stomach in response to food intake to allow the storage of the ingested meal. Indeed, this physiologic phenomenon induced by gastric distention prevents the rise in gastric wall tension during food consumption. Meal ingestion, therefore, causes a drop in intra-gastric pressure (IGP) followed by a steady recovery until baseline values in parallel with the appearance of a feeling of satiation (Hunt et al., 2015). The change in IGP following a meal is used as a surrogate marker for gastric accommodation in research (Pauwels et al., 2014). This mechanism is altered in a subgroup of FD patients and associated with early satiation (Tack et al., 1998).

Gastric motility is altered in patients with FD. Different methods can be used to assess GE in clinical practice, mainly GE scintigraphy and ^{13}C -octanoic-acid breath testing (see Chapter 4.5. Assessment of gastric emptying). Slower GE has been described in about 40% of patients with FD (Quartero et al., 1998). Assessing GE in all patients with dyspepsia is not recommended (Wauters et al., 2021b), except in the presence of severity criteria (vomiting, weight loss, etc.). Indeed, the link between GE and dyspeptic symptoms is debated (Talley et al., 2006b,

Vijayvargiya et al., 2019) and does not guide therapeutic choices. The propagation velocity of antral peristalsis is also significantly lower in FD patients compared to healthy controls (Sclocco et al., 2022). Gastric dysrhythmias are found in about two thirds of FD patients following meal ingestion (Koch et al., 2023). Small intestinal motor abnormalities have also been described in FD (Jebbink et al., 1996).

Visceral hypersensitivity is the perception of non-painful or physiologic stimuli in the gut as discomfort or pain. Hypersensitivity to gastric distension is also present in a subset of FD patients (Mearin et al., 1991) and is associated with postprandial epigastric pain (Tack et al., 2001). Fasting and postprandial hypersensitivities in another study are more frequent in the PDS subtype (Di Stefano et al., 2014). The importance of visceral hypersensitivity is discussed later in this introduction (see Visceral hypersensitivity). Conversely, about 5% of patients have decreased sensitivity to gastric distention, diagnosed as a discomfort threshold during a barostat study above the mean plus two standard deviations (SD) (Tack et al., 2001).

An **impaired autonomic function** has also been described in a subset of FD patients (Ali and Chen, 2023). Heart rate variability (HRV), defined by the changes in R-R intervals between heartbeats measured on an electrocardiogram (ECG), can be divided into ultra-low-frequency (ULF), very-low-frequency (VLF), low-frequency (LF, 0.05-0.15 Hz), and high-frequency (HF, 0.15-0.5 Hz) bands (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). The ratio between LF, reflecting sympathetic activity, and HF, reflecting parasympathetic activity, bands (LF/HF ratio, %) is a measure of the sympatho-vagal balance, one of the most commonly used metrics of HRV (Shaffer and Ginsberg, 2017). Based on 24-hour HRV and cardiovascular reflex tests, a decreased efferent vagal activity is found in up to 30.4% of FD patients with PDS (Lorena et al., 2002b).

Food ingestion is a significant trigger for dyspeptic symptoms (Duncanson et al., 2018). An inverse association between meal frequency and the prevalence of FD has been described in the population (Hassanzadeh et al., 2016). There is also an association between masticatory performance and the presence of FD (Carretero et al., 2011). Reduced fat intake has also been reported in FD (Carvalho et al., 2010), however, dietary habits do not necessarily play a causal role in FD development. Indeed, patients are likely to adapt their food intake patterns to decrease symptom occurrence and severity in this disorder. Still, food also induces

local immune reactions in the duodenum, as shown by confocal laser endomicroscopy following the local administration of food proteins and the improvement of symptoms with a six-food elimination diet (egg, fish/shellfish, milk, nuts, soy, and wheat) in FD patients (Van den Houte et al., 2022).

New evidence shows that FD is also a **duodenal disorder**. Increased spontaneous duodenal acid exposure has been described in FD (Lee et al., 2004a), whereas the infusion of lipids in the duodenum induces dyspeptic complaints (Feinle et al., 2001). Low-grade inflammation is found in the duodenal mucosa, with increased numbers of activated eosinophils and mast cells (Walker et al., 2009, Walker et al., 2010, Vanheel et al., 2014), intra-epithelial lymphocytes (Gargala et al., 2007), and a higher density of cholinergic tuft cells (Huang et al., 2022b). Besides increased duodenal eosinophils in FD patients compared to controls, especially in PI-FD, degranulation of duodenal eosinophils is also increased (Shah et al., 2022). Increased duodenal permeability and dysbiosis (Vanheel et al., 2014, Wauters et al., 2021a) have also been described in FD. Duodenal alterations could affect the sensorimotor function of the stomach (GE, impaired accommodation and hypersensitivity to distension) through duodeno-gastric reflex pathways (Lee et al., 2004b).

Even if there is no gross inflammatory process in FD, systemic and local **immune activations** have also been described in the disorder, especially altered local immune responses (Burns et al., 2019). A shift towards Th2 and Th17 T cell responses (vs Th1) has been described in the duodenal mucosa of FD patients compared to controls (Burns et al., 2022). Th17 cells are a subset of CD4⁺ T cells that secrete several cytokines, affecting immune homeostasis and inflammation (Rossi and Bot, 2013). The presence of effector and memory cells suggests that this micro-inflammation is antigen-driven, candidate triggers being bacteria and dietary antigens. The hypothesis is that increased permeability in the duodenum and proximal small intestine could induce local immune activation via antigens present in the lumen, with secondary infiltration by eosinophils and mast cells (Wauters et al., 2020). No change in T cell populations from the peripheral blood was found in FD patients compared to controls (Burns et al., 2022) but increased circulating $\alpha 4\beta 7^{+}$ gut-homing T cells have been described (Burns et al., 2019).

Connections between duodenal mucosa-associated **microbiota** and both GE and dyspeptic symptoms have recently been found in FD (Shanahan et al., 2022): a negative correlation was observed between the relative abundance of

the genus *Veillonella* and gastric half-emptying time ($T_{1/2}$), whereas the relative abundance of taxa affiliated with the *Firmicutes* increased, and taxa affiliated with the *Bacteroidota* decreased with symptom burden. Dysbiosis, an imbalance of the gut microbiota with reduced microbial diversity, could, therefore, play a role in the pathophysiology of the disorder due to an altered microbiota-gut-brain axis (Rupp and Stengel, 2022). Changes in the microbiota could also be secondary to dietary and physiological modifications in the disorder, however (Wuestenberghs et al., 2018).

Psychological factors such as anxiety and depression are also prevalent in FD (Esterita et al., 2021). Anxiety is associated with an increased risk of developing FD over time (Aro et al., 2015). Indeed, psychological distress is involved in the development of DGBI (Koloski et al., 2016). Brain-gut pathways are bidirectional, but the mood disorder preceded the DGBI in two-thirds of the cases and followed the development of the DGBI in only one-third of the patients in a one-year prospective study (Koloski et al., 2016). Psychological factors can also alter the sensorimotor function of the stomach since fundic accommodation can be altered experimentally by anxiety in healthy subjects (Geeraerts et al., 2005). Patients suffering from FD also have greater somatisation, especially those with PDS-EPS overlap (Aziz et al., 2018a).

Finally, the **central processing** of signals from the gastroduodenal region is also involved in the pathophysiology of the disorder. Indeed, altered brain processing of GI stimuli has been reported (Kanazawa et al., 2000). An altered structural and functional connectivity of the insula, which is involved in visceral pain processing and the affective response to it, is described in most functional magnetic resonance imaging (fMRI) studies in FD patients (Liu et al., 2017, Liu et al., 2018, Sclocco et al., 2022). Functional connectivity between brainstem nuclei (nucleus tractus solitarii [NTS], carrying afferent sensory information from the stomach through the vagus nerve) and cortical areas is altered in FD patients, which is correlated with lower antral peristaltic propagation velocity, suggesting an altered gut-brain axis in the disorder in relation to neural plasticity (Sclocco et al., 2022). Neuroplasticity is defined as the ability of the brain to change neural networks, from the level of an individual neuron to the level of the entire cortex (e.g. cortical remapping following an amputation). Resting-state fMRI data suggests that altered connectivity of the periaqueductal grey matter might be associated with the abnormal modulation of pain and emotions in FD patients (Liu

et al., 2017). Life stress is one of the most important predictors of FD status (Bennett et al., 1991). Abuse history has been shown to affect directly somatic symptoms reporting by FD patients (Jones et al., 2013a). Patients with FD have a higher negative perception of adverse life events than controls (Hui et al., 1991).

Diagnosis

There is no biomarker for the disorder. The first step in diagnosing FD, and its subdivision into PDS and EPS, is to recognise dyspeptic symptoms through history taking or using questionnaires based on Rome criteria. Accurate **symptom reporting** by patients is complex, however, with cultural and linguistic influences on patients' understanding of the terms (Fujikawa et al., 2017). The Rome criteria may need to be validated in Asia, for example (Miwa et al., 2012). Adding pictograms to verbal descriptors has demonstrated improvement in symptom reporting (Tack et al., 2014). It is also necessary to bear in mind that there is a systematic bias favouring the diagnosis of GORD over that of FD in primary care (Pleyer et al., 2014).

Since functional and organic dyspepsia cannot be differentiated according to symptoms, an **upper GI endoscopy** is necessary for the definite diagnosis of FD, which remains a diagnosis of exclusion. In primary care, however, uninvestigated dyspepsia can be tested for *H. pylori* infection without performing an endoscopy, or empirical therapy with a proton pump inhibitor (PPI) may be preferred, in the absence of alarm symptoms or risk factors for organic diseases, especially gastric cancer (*test-and-treat* strategy), and taking into account the patient's age, ethnicity, and the local prevalence of *H. pylori* infection (Moayyedi, 2002). Conversely, alarm symptoms should prompt endoscopy even in younger patients. Patients at higher risk for malignancy include those who spent their childhood in a country with a higher risk of gastric cancer, such as Mongolia, China and Bolivia (Song et al., 2022), and those with a positive family history of gastric cancer, in particular. Given the increased risk of pancreatic cancer in elderly patients, North American guidelines suggest adding pancreatic imaging to endoscopy in the workup of patients presenting with new-onset EPS symptoms over 60 (Moayyedi et al., 2017).

No **other testing**, such as upper abdominal ultrasound, GE testing and oesophageal pH monitoring to rule out GORD, is required in routine care to retain a diagnosis of FD (Wauters et al., 2021b).

Prognosis

Functional dyspepsia is a **benign disorder** and is not associated with increased mortality in the community. Indeed, dyspepsia at study entry did not affect survival over more than 84,000 years of follow-up in a large cohort of over 8,300 individuals (Ford et al., 2012).

The prevalence of FD remains stable over time in cohort studies, but there is a high turnover of symptoms and diagnoses over ten years (Halder et al., 2007, Olafsdottir et al., 2012).

Functional dyspepsia is responsible for direct and indirect **costs**, both for society and patients: medical consultations, diagnostic tests, co-financed treatments, over-the-counter medications, alternative and complementary therapies, dietary modifications, absenteeism and loss of productivity at work (Nyrén et al., 1992, Moayyedi and Mason, 2002, Lacy et al., 2013).

Quality of life (QoL) is discussed in Chapter 4.4. Assessment of quality of life in disorders of gut-brain interactions. Functional dyspepsia is associated with reduced QoL (Aziz et al., 2018a). An older study found that FD affects all main domains (physical, mental and social) of health-related QoL (HR-QoL) in the general population (Aro et al., 2011). Quality of life is more impaired in patients with FD than in those with chronic liver disease, for instance (Haag et al., 2008). Factors associated with a more significant loss of QoL in FD patients include anxiety and depression levels, advanced age, female gender, symptom severity, low or intermediate cultural level, and sleep disturbance (Hantoro et al., 2018). Functional dyspepsia is also associated with lower exercise levels in the general population (Koloski et al., 2020, Furukawa et al., 2022), sleep disturbance (Lacy et al., 2011) and sexual dysfunction (Fass et al., 1998). Conversely, exercising with groups and friends, but not alone, is inversely associated with FD (Furukawa et al., 2022).

Weight loss is considered an alarm symptom (Jones et al., 2008), but can be a consequence of FD in a subset of subjects (loss of > 5% of original body

weight in up to 56.6% of tertiary care patients (Schol et al., 2022)). It is associated with early satiation (Tack et al., 2010) and PI-FD (Schol et al., 2022).

Healthcare-seeking behaviour in FD is driven by the impact of symptom severity and psychosocial comorbidities (higher anxiety and depression scores) (Haycox et al., 1999, Hu et al., 2002).

Treatment

The treatment of FD is challenging and remains disappointing for most patients (Vandenberghe et al., 2010). A good patient-provider relationship and **reassurance** are essential for an optimal management (Drossman et al., 2021).

Despite the lack of controlled **dietary** interventional studies, patients are advised to take frequent small-size meals and to avoid high-fat food items (Pilichiewicz et al., 2009, Duboc et al., 2020). A low-FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) diet is similarly efficacious as traditional dietary advice, especially in the PDS subtype (Goyal et al., 2022). Correction of dyssynergic defaecation by biofeedback therapy reduces dyspeptic complaints in patients with PDS also suffering from constipation with functional defaecation disorder (Huaman et al., 2020).

Once-daily **PPI therapy** for 4-8 weeks is currently the first-line treatment since it is more effective than placebo in the reduction of global symptoms of FD (relative risk of remaining dyspeptic is 0.88 [95% CI: 0.82-0.94]; NNT of 13) (Pinto-Sanchez et al., 2017). This therapeutic class acts at the duodenal level in FD patients: indirectly by reducing the acid burden arriving at it and directly by reducing duodenal eosinophils, mast cells and paracellular permeability (Wauters et al., 2021a). Still, it treats the possibly associated gastro-oesophageal reflux (GOR) and unrecognised gastro-duodenal peptic complication. Similarly, histamine-2 receptor antagonists are also an efficacious therapy but with a lower level of evidence compared to PPI (Ford et al., 2021).

Prokinetics are also effective in alleviating dyspeptic symptoms, with a relative risk of remaining dyspeptic of 0.81 (95% CI: 0.74-0.89) and a NNT of 7 (12 if studies with cisapride are excluded) (Pittayanon et al., 2019). The evidence needs improvement, however, and no target subgroup has been identified. The most frequently used prokinetics in this disorder are domperidone and acotiamide. Itopride, a combined dopamine receptor D2 antagonist and

acetylcholinesterase inhibitor, has also shown some efficacy, with a positive Phase IIb trial (Holtmann et al., 2006), but three negative Phase III trials (Talley et al., 2008, Carbone et al., 2022b).

Psychotropic drugs (mainly tricyclic antidepressants and antipsychotics) have a beneficial effect, with a relative risk of remaining dyspeptic being 0.78 (95% CI: 0.68-0.91) and a NNT of 6 (Ford et al., 2017). For instance, amitriptyline relieves symptoms in some patients, particularly in the EPS subtype (Talley et al., 2015). Still, this effect is not due to altered perception thresholds following gastric distension or improved sleep, but is likely due to a better tolerance to uncomfortable visceral sensations (Mertz et al., 1998a). Tricyclics were ranked first for efficacy in a network meta-analysis when only randomised controlled trials (RCT) with low risk of bias were included, with a relative risk of remaining dyspeptic of 0.71 (95% CI: 0.58-0.87) (Ford et al., 2021). Mirtazapine has also been shown to improve early satiation, nutrient tolerance and weight in patients with weight loss (Tack et al., 2016a).

Some other drugs also improve symptoms compared to placebo: **buspirone**, by improving fundic accommodation despite delaying GE of liquids in treated patients (Tack et al., 2012); a combination of **peppermint and caraway oils** (Rich et al., 2017, Madisch et al., 2022); **sulpiride and levosulpiride** in low-quality trials involving small sample sizes (Ford et al., 2021); and **rikkunshito**, a traditional Kampo medicine treatment, in Japanese (Suzuki et al., 2014) but not Belgian subjects (Masuy et al., 2020). Spore-forming **probiotics** (a combination of *Bacillus coagulans* MY01 and *B. subtilis* MY02) have also shown promising results, with 48.0% of clinical responders compared to 20.0% in the placebo group in the per-protocol analysis ($p = 0.028$) in a single-centre RCT (Wauters et al., 2021c).

Psychological interventions, especially cognitive behavioural therapy, could have a sustained benefit for dyspeptic symptoms, but the evidence is scarce (Soo et al., 2005, Dehghanizade et al., 2015). Psychodynamic interpersonal psychotherapy has shown benefits on symptom scores both on the short- and the long-term in patients with refractory FD (Hamilton et al., 2000). A psychotherapy using group and individual sessions focused on teaching techniques for coping with FD also improves outcomes when added to standard medical therapy (Orive et al., 2015).

Enhancement of vagal activity by **transcutaneous auricular vagal nerve stimulation** (ta-VNS) improves gastric accommodation, gastric pace-making activity and postprandial symptoms in non-severe FD patients (Zhu et al., 2021).

Finally, **enteral and parenteral feedings** are sometimes necessary for the most severe patients to maintain their nutritional status.

Functional dyspepsia, like all other DGBI, is a complex disorder. The association of the disorder with different comorbidities adds a layer of complexity and will be the subject of the following two subchapters.

1.2. Main comorbidities associated with functional dyspepsia

Functional dyspepsia frequently overlaps with GORD and IBS, two highly prevalent DGBI. Overlap syndromes are associated with impaired QoL, more severe symptoms and worse outcomes in dyspepsia (Gwee et al., 2008). Patients with FD also frequently present other comorbidities, such as anxiety and depression. Over time, there is an increasing awareness of the importance of taking them into account, as exemplified by the 2016 recommendation to assess overlaps, comorbidities and disease modifiers in the design of clinical trials concerning FD (Irvine et al., 2016).

There is no consensus regarding categorising “comorbidities” associated with FD. We propose classifying them arbitrarily into four groups: (1) overlaps with organic diseases (*H. pylori* infection, diabetes mellitus, gastroparesis, etc.); (2) overlaps with other DGBI (GORD, IBS, etc.); (3) overlaps with non-GI functional somatic syndromes (fibromyalgia, chronic fatigue syndrome (CFS), migraine, bladder pain syndrome (BPS), etc.) and (4) psychological factors (anxiety, depression, stress, somatisation, sleep disorders, etc.).

The list of comorbidities described in this chapter is not exhaustive. We have limited the description to the most commonly described and challenging conditions from this “never-ending list”. Arbitrary choices were needed to classify some comorbidities into a particular category; for example, bruxism and restless leg syndrome have been classified as non-GI functional somatic disorders given the frequency of central sensitisation in these disorders, but they could also have been classified among sleep disorders.

Overlaps with organic diseases

Overlaps with organic diseases are essential to assess for different reasons: it helps to know whether or not these entities are independent of FD (gastroparesis, *H. pylori* gastritis, diabetic gastroenteropathy, etc.), these diseases sometimes do part of the differential diagnosis of FD (biliopancreatic diseases, food intolerances, etc.), and this sheds light on the pathophysiology of FD (immune and neuromuscular disorders, dysbiosis, etc.).

Gastroparesis

Gastroparesis is defined by the association of upper GI symptoms with delayed GE without the mechanical obstruction of the stomach (Parkman et al., 2010). Cardinal symptoms are nausea and vomiting, but symptoms of PDS are frequently encountered (Schol et al., 2021). Functional dyspepsia is associated with delayed GE in about one-third of the cases (Stanghellini et al., 1996, Talley et al., 2006a). A meta-analysis found the GE of solids in FD patients to be 1.5 times slower than in healthy controls and a significant delay in emptying in almost 40% of those patients (Quarero et al., 1998). The distinction between idiopathic gastroparesis and FD with delayed GE is still debated, with differences between Europe and the United States of America (USA) (Parkman et al., 2010). Theoretically, patients with the PDS subtype of FD and impaired GE could be diagnosed with idiopathic gastroparesis. Indeed, both entities are indistinguishable based on clinical and physiologic features (Pasricha et al., 2021), suggesting that they should be considered part of the same spectrum. In everyday life, misdiagnoses of gastroparesis are common, probably linked with an under-recognition of FD (Cangemi et al., 2023). However, gastroparesis is clearly distinguished from FD and its PDS subtype in the recent European consensus (Schol et al., 2021). Care must be taken not to label erroneously a FD patient as gastroparetic as this will mark them for life and could lead to inappropriate invasive procedures, like gastric per-oral endoscopic myotomy (G-POEM) (Quigley, 2023).

Diabetes mellitus

Diabetes mellitus is a metabolic disorder characterised by chronic hyperglycaemia. A subgroup of patients with diabetes suffers from FD-like

symptoms. Diabetes mellitus is a cause of secondary dyspepsia since metabolic disorders are an exclusion criterion for the diagnosis of FD according to Rome criteria (Stanghellini et al., 2016). The prevalence of FD and the high rate of undiagnosed diabetes in the general population (Langholz et al., 2021), however, make it likely that diagnoses of FD are being made for patients with diabetes, especially since recent European and American consensus papers do not include fasting glycaemia in the workup of patients with dyspepsia (Moayyedi et al., 2017, Wauters et al., 2021b). On the other hand, the prevalence of FD in the general population also makes it likely that some patients with diabetes mellitus have upper GI symptoms linked to “true” FD. Discriminating FD from symptoms caused by GI dysfunction resulting from diabetes has been impossible until now. Indeed, FD-like symptoms are not always related to persistent delayed GE since the same complaints can also occur in patients with normal or even rapid GE; impaired gastric accommodation and visceral hypersensitivity of the stomach are critical factors in explaining symptoms (Kumar et al., 2008). The term **"diabetic gastroenteropathy"** encompasses all the GI manifestations of diabetes mellitus, while **"diabetic gastroparesis"** is restricted to patients with moderate to severe dyspeptic symptoms associated with delayed GE.

Autoimmune diseases

Autoimmune diseases are defined by an abnormal immune response directed against one's own body. There are numerous autoimmune diseases, with the main being type 1 diabetes, thyroidal diseases (Graves' disease and Hashimoto's thyroiditis), rheumatoid arthritis, Sjögren's syndrome, lupus, autoimmune gastritis and coeliac disease, among others. The last two will be treated in separate subchapters. Any autoimmune disorder has been reported in 4.8% of FD patients (Ford et al., 2014).

Autoimmune and inflammatory connective tissue diseases include Sjögren's syndrome, affecting mainly lacrimal and salivary glands, rheumatoid arthritis, affecting mainly joints, and systemic lupus erythematosus, affecting different parts of the body. There is no data on the association between FD and **Sjögren's syndrome**, even if upper abdominal pain was reported by 54% of patients suffering from this autoimmune disease (Parreau et al., 2021). **Rheumatoid arthritis** was reported in 8.5% of FD patients (Koloski et al., 2019).

Functional dyspepsia was reported in 72.7% of female Mexican patients suffering from **systemic lupus erythematosus** (García-Carrasco et al., 2018).

Systemic sclerosis, formerly called scleroderma, is a systemic inflammatory condition of autoimmune origin affecting the skin and other organs, especially the GI tract. The involvement of the GI tract affects mainly the esophagus and the stomach, with delayed gastric emptying and dyspeptic complaints (Marie et al., 2012). It is therefore a cause of secondary dyspepsia.

Chronic gastritis

Helicobacter pylori infection induces chronic gastritis. Dyspeptic patients suffering from *H. pylori* gastritis may benefit from eradication therapy (Mazzoleni et al., 2011), with a reduction of symptoms in some patients after 6-12 months (Malfertheiner et al., 2003), which suggests a causal link between the infection and dyspeptic symptoms, with the NNT being 15 (Kang et al., 2019). All patients with dyspepsia should therefore be tested for *H. pylori* (Wauters et al., 2021b). Since no marker predicts the response to eradication, and *H. pylori* gastritis is considered an infectious disease (Sugano et al., 2015), all patients identified with *H. pylori* gastritis should be treated (Wauters et al., 2021b). If symptoms resolve after eradication therapy, the diagnosis would be retrospectively “***H. pylori*-associated dyspepsia**” (Sugano et al., 2015). Conversely, if symptoms persist 6-12 months after confirmed eradication, a diagnosis of FD can be made (Wauters et al., 2021b).

Chronic gastritis is a histological diagnosis defined by inflammation of the gastric mucosa with signs of chronicity, irrespective of the underlying cause. On the contrary, FD is diagnosed in the presence of specific symptoms. The leading causes of chronic gastritis are *H. pylori* gastritis and, to a lesser extent, autoimmune gastritis. There is frequently the development over time of atrophic gastritis, defined by the loss of gastric glands, with or without intestinal metaplasia, a preneoplastic condition of the stomach (Correa et al., 1975). The existence of intestinal metaplasia almost always implies the presence of atrophic gastritis. If the diagnosis of **autoimmune gastritis**, also named **pernicious anaemia**, is suspected, the workup should include checking anti-parietal cells and anti-intrinsic factor antibodies, and looking for anaemia and deficiencies in vitamin B12 and iron. Autoimmune gastritis is associated in ~60% of the cases with GI symptoms, mainly dyspepsia and PDS (Carabotti et al., 2017).

Gluten-related disorders

Coeliac disease is an autoimmune enteropathy triggered by gluten consumption in genetically predisposed individuals. The proportion of subjects who were seropositive for tissue transglutaminase IgA antibodies was 5.9% with dyspepsia, 4.0% in IBS, and 2.6% in asymptomatic controls (all $p > 0.05$) in a population-based case-control study from Olmsted County (USA), among residents aged 20 to 50 years (Locke et al., 2004a). Similarly, the prevalences of positive coeliac serology and biopsy-proven coeliac disease following positive serology were higher in subjects with dyspepsia compared to healthy subjects (3.2 vs 1.3%), but without statistical significance (odds ratio (OR) 2.85 [95% CI: 0.60-13.38]), in a meta-analysis (Ford et al., 2009). The prevalence of coeliac disease was even lower (1.1%) in Indian patients with uninvestigated dyspepsia (Sharma et al., 2015). Coeliac disease was, however, significantly associated with a diagnosis of FD in the Australian population (OR 3.35 [95% CI: 1.72-6.52]) (Potter et al., 2018).

Non-coeliac gluten/wheat sensitivity (NCGS) is an undefined disorder lacking validated diagnostic criteria in which patients describe symptoms induced by gluten/wheat ingestion and improved by limiting gluten/wheat consumption in the absence of coeliac disease or wheat allergy (Reese et al., 2018). This entity was reported by 8.2% of FD patients in a population-based study (Zand Irani et al., 2021) and diagnosed in 6.4% of patients with refractory FD in a RCT with a long gluten-free diet followed by blinded gluten ingestion (Shahbazkhani et al., 2020). The disorder was independently associated with FD (OR 1.48 [95% CI: 1.13-1.94]) in the Australian population (Potter et al., 2018). The proportions of FD patients with self-reported wheat sensitivity were even higher, with a range of 23.8-25.3%, in this study.

Atopy

Atopy is the genetic predisposition to produce an exaggerated immunoglobulin E (IgE) immune response to otherwise harmless substances in the environment, characterised by the simultaneous development of common **allergic conditions** (atopic dermatitis, asthma and allergic rhinitis). White blood cells involved in allergic reactions are mast cells, eosinophils and basophils. Asthma (OR 1.32 [95% CI: 1.04-1.68]) and food allergy diagnosed by a physician

(OR 1.78 [95% CI: 1.28-2.49]) were independent predictors of FD in the general population (Koloski et al., 2019). Eczema, hay fever/rhinitis and allergic conjunctivitis were reported in 27.5%, 7.8% and 3.1% of FD patients, respectively (Jones et al., 2014). Functional dyspepsia was independently associated with **asthma** (OR 3.02 [95% CI: 1.44-6.34]), but not atopic dermatitis and allergic rhinitis (Zand Irani et al., 2021).

Mastocytosis and associated disorders

Mast cells are a variety of white blood cells responsible for allergic reactions, anaphylaxis and immune tolerance, and express the surface receptor CD117 (c-kit, encoded by the *KIT* gene).

Mastocytosis includes cutaneous mastocytosis, systemic mastocytosis, mast cell leukaemia, hereditary alpha tryptasemia and mast cell activation syndrome (Beyens et al., 2022). These conditions are characterised by the overgrowth of mast cells and the occurrence of episodes that mimic allergic reactions, due to the release of mast cell mediators, especially histamine.

Cutaneous mastocytosis and **systemic mastocytosis** are clonal proliferations of mast cells in the skin and different organs, respectively, the first having no systemic manifestations. Systemic mastocytosis is associated with an acquired mutation in the *KIT* gene (D816V).

Hereditary alpha tryptasemia (HαT) is a newly-described condition defined by increased copies of the germline *TPSAB1* gene, coding for α-tryptase (Lyons, 2018). This genetic trait affects ~5% of the Western population and is the leading cause of elevated basal serum tryptase (Robey et al., 2020). The condition has a variable clinical penetrance: subjects carrying extra copies of the α-tryptase gene can be asymptomatic, but others have symptoms, including diarrhoea (in more than one-third of the subjects), skin flushing (~40%), urticaria/angio-oedema (in half of the cases), and food intolerances (~40%), among others (Robey et al., 2020). The condition can be suspected when an increased density of mast cells is described on duodenal biopsies and in case of elevated basal serum tryptase (> 8 ng/mL). Still, genetic testing is mandatory for a definite diagnosis. Carriers of HαT have a genetic predisposition to anaphylaxis, especially in the case of systemic mastocytosis (Greiner et al., 2021). No data is available in FD patients, but its prevalence in a cohort of IBS patients was 5% (Konnikova et al., 2021). The condition could be distinguished from IBS by an increased mast cell number and

intestinal epithelial cell pyroptosis, a form of programmed cell death, in the small intestine, and class-switched memory B cells in both the gut and peripheral blood associated with IgG reactive to GI-related proteins (Konnikova et al., 2021).

Mast cell activation syndrome (MCAS) is a controversial multi-system disorder caused by non-clonal mast cell activation (Weinstock et al., 2021). The diagnosis is based on (1) "typical" symptoms in conjunction with (2) an increase in a mast cell mediator (serum tryptase or 24-hour urine test for metabolites of histamine and prostaglandin D2) over baseline during a period of increased symptoms, and (3) > 50% reduction in symptoms with medications blocking mast cell mediators (H1-antihistamines, sodium cromoglycate, etc.) (Valent et al., 2012). Typical symptoms include (near-)syncope, flushing, shortness of breath, diarrhoea, etc. (Weiler et al., 2019). Symptoms suggesting MCAS in ≥ 2 organ systems out of four (cardiovascular, dermatologic, respiratory and gastrointestinal) occurring concomitantly were reported by 85% of patients referred for DGBI in a tertiary care setting (Wilder-Smith et al., 2019). The median number of MCAS symptoms was 6 [interquartile range: 4-8] in FD patients (Wilder-Smith et al., 2019). The significant overlap of symptoms between MCAS and DGBI makes it necessary to use the additional criteria and not symptoms alone to avoid MCAS misdiagnoses in patients with DGBI.

Eosinophilic gastrointestinal disorders

Eosinophils are a variety of white blood cells responsible for the immune response to parasites and allergic reactions, together with basophils.

Eosinophilic GI disorders (EGIDs), an umbrella term, include **eosinophilic oesophagitis (EoE)**, **eosinophilic gastritis**, **eosinophilic enteritis** and **eosinophilic colitis** (Dellon et al., 2022). If multiple levels of the gut are involved, the name of the primary location is used, considering the predominant symptoms and endoscopic features. No data in FD patients is available.

Hypermobility spectrum disorders

Hypermobility spectrum disorders is the generic term grouping all the disorders presenting with joint hypermobility. Among them, hereditary non-inflammatory connective tissue disorders include **Ehlers-Danlos syndromes (EDS)**, caused mainly by mutations in collagen genes, and **Marfan syndrome**, caused by a mutation in the fibrillin-1 (*FBN1*) gene, among others. The EDS are a

heterogeneous group of disorders characterised by joint hypermobility, skin hyperextensibility, and tissue fragility, with 13 subtypes described in the new 2017 international classification (Malfait et al., 2017). A genetic basis for all the subtypes has been described, except for the **hypermobile subtype (hEDS)**, which is also the most common. The terminologies "joint hypermobility syndrome" (JHS) (Beighton et al., 1988), "EDS type III", or "EDS, hypermobility type" (EDS-HT) according to the Villefranche nosology (Beighton et al., 1998) are outdated and all substituted by the term hEDS in the new nomenclature of the International Ehlers-Danlos Syndrome Consortium (Castori et al., 2017). The hypermobility of a joint is established by measuring the range of motion of this joint and comparing it with normal values. Joint hypermobility can be localised, affecting no more than five joints, or generalised, affecting joints at multiple sites. The term "hypermobility spectrum disorder" describes individuals with symptomatic joint hypermobility who don't satisfy the criteria for a specific syndrome (Castori et al., 2017).

Patients with EDS frequently complain of GI symptoms and can suffer from GI dysmotility, especially delayed GE and altered colon transit times (Nelson et al., 2015, Alomari et al., 2020, Lam et al., 2023). In an anonymous web-based cross-sectional study, functional dyspepsia based on Rome III criteria was present in 55.4% of patients with EDS and 25.0% of patients with Marfan syndrome (Nee et al., 2019). The prevalence of JHS is higher in patients with PDS compared to those with organic GI disorders (51.0 vs 27.5%, OR 1.99 [95% CI: 1.06-3.76]) (Fikree et al., 2015). Another study found JHS in 54% of FD patients compared to 7% of healthy controls (Carbone et al., 2021).

Small intestinal bacterial overgrowth

Small intestinal bacterial overgrowth (SIBO) is an excess of bacteria in the small bowel, and the gold standard for its diagnosis is the culture of jejunal aspirates. Surrogate tests for diagnosis are glucose and lactulose breath tests, with low sensitivity in subjects without predisposing conditions, such as a history of surgical reconstruction of the GI tract. The sensitivity of the glucose breath test for SIBO diagnosis is about 40%, which is, however, better than the sensitivity of the lactulose breath test (Losurdo et al., 2020). The prevalence of SIBO was significantly higher in FD subjects compared to healthy subjects (19.4 vs 3.3%, $p = 0.037$) and similar to IBS subjects (19.4 vs 16.7%, $p = 0.63$) in one study (Tziatzios

et al., 2021). Another study found a prevalence of 71.4% (Liu et al., 2021). A third study using lactulose breath testing found SIBO in 48.6% of patients with PDS and 47.6% of those with EPS (Chojnacki et al., 2020). However, the link between FD and SIBO is still debatable (Gurusamy et al., 2021), as well as whether it should be considered a disease entity or a pathophysiological mechanism.

Sugar malabsorption and intolerance

There may be some overlap between lactose or fructose intolerances and FD symptoms. Indeed, symptoms such as bloating and nausea are shared by both conditions. Malabsorption is defined by the impaired absorption of a sugar, highlighted by increased hydrogen/methane (H_2/CH_4) excretion in breath samples during breath tests. In contrast, intolerance is defined by positive symptom induction after ingestion of this sugar (Bouchoucha et al., 2021). The two most assessed sugars in clinical practice are lactose and fructose.

Milk challenge, H_2/CH_4 breath testing or LCT-13910C/T genotyping, the most frequent single nucleotide polymorphism (SNP) located upstream of the lactase gene (LCT) and linked to lactase activity, are all used to diagnose **lactose malabsorption or intolerance** associated with adult-type hypolactasia. Milk intolerance was reported by 48.5% of FD patients vs 64.2% of those without the disorder ($p < 0.001$) (Nakov et al., 2020). Lactose malabsorption was found in 30.8% of patients with FD, while malabsorption with intolerance was only found in 27.8% (Wilder-Smith et al., 2013). In this study, lactose intolerance, irrespective of lactose malabsorption or not, was reported by 49.7% of the patients (Wilder-Smith et al., 2013). Based on the genotyping, another study found adult-type hypolactasia to be present in 44.7% of patients with FD (Wortmann et al., 2018), with similar symptoms between patients with FD with or without lactose intolerance except for bloating, which could therefore serve as a marker to assess adult-type hypolactasia in this population.

The proportion of FD patients with **fructose malabsorption** was 52.7% in one study, but varied from $< 35\%$ to $> 60\%$ depending on the ethnic group (Mishkin et al., 1997). There is no data about **fructose intolerance** in FD patients.

Biliopancreatic diseases

A meta-analysis found no association between the presence of **gallstones** and dyspeptic symptoms (except nausea and vomiting) (Kraag et al., 1995).

Patients with gallstones who underwent cholecystectomy for symptomatic gallstone disease more frequently experience the persistence of non-biliary abdominal pain post-cholecystectomy if they fulfil the criteria for FD before surgery (de Jong et al., 2022), which suggests that both disorders behave separately. The old concept of “gallstone dyspepsia” should therefore be avoided. Performing an abdominal ultrasound to exclude gallstones systematically in patients with FD without biliary colic is not recommended (Wauters et al., 2021b).

Gallbladder dysmotility has been reported in some FD patients. However, there is a discrepancy in the results of studies evaluating gallbladder emptying in patients with FD (Misra et al., 1991, Marzio et al., 1992, Liu et al., 1995), with only some of them reporting gallbladder hypokinesia, and no conclusion can be drawn. Levosulpiride has been shown to accelerate gallbladder emptying and to improve dyspeptic symptoms in a randomised double-blinded study which was not designed to establish a cause-and-effect relationship (Arienti et al., 1994).

Dyspeptic symptoms are uncommon in **chronic pancreatitis** (Gullo et al., 1995). However, **exocrine pancreatic insufficiency** has been reported in patients with dyspepsia (Andersen et al., 1982, Smith et al., 1991), especially those resistant to PPI (Fujikawa et al., 2017), from 27 to 71% of the cases. Morphological signs of chronic pancreatitis were also frequent in patients with epigastric pain syndrome-like symptoms (Lariño-Noia et al., 2018). Indeed, dyspepsia has been associated with mild chronic pancreatitis diagnosed by endoscopic ultrasonography (EUS) (Sahai et al., 2000). More recently, **early chronic pancreatitis**, defined as the stage of chronic pancreatitis with preserved pancreatic function, was diagnosed in 64% of patients with EPS associated with pancreatic enzyme abnormalities (Hashimoto et al., 2017). 24.5% of patients with FD resistant to PPI therapy were also diagnosed with early chronic pancreatitis using EUS in a Japanese study (Wakabayashi et al., 2018). However, diagnosing early chronic pancreatitis on solely morphological grounds does not seem possible (Whitcomb et al., 2018); future studies must clarify the link between FD and this new disorder.

Superior mesenteric artery syndrome

Superior mesenteric artery syndrome, or Wilkie's syndrome, is due to the compression of the third segment of the duodenum between the superior mesenteric artery and the aorta. It is a rare cause of gastric outlet obstruction,

accounting for 0.005% of all upper GI endoscopies (Sinagra et al., 2018). The diagnosis is usually suspected when a pulsatile extrinsic compression of the third portion of the duodenum is seen during endoscopy. However, an angle between the superior mesenteric artery and the aorta measured below 22° at imaging is necessary for the diagnosis. The disorder is described in case series, especially in patients with eating disorders. It seems to be linked to undernutrition and rapid weight loss, leading to the disappearance of the mesenteric fat pad (Storm et al., 2022). No systematic reporting of angulation has been described in FD patients. However, about 70% of the patients with this syndrome report PDS symptoms (Sinagra et al., 2018).

Oesophageal motility disorders

Oesophageal motility disorders include disorders of oesophagogastric junction (OGJ) outflow (achalasia and OGJ outflow obstruction (OGJO)) and disorders of peristalsis (absent contractility, distal oesophageal spasm, hypercontractile oesophagus and ineffective oesophageal motility) (Yadlapati et al., 2021). Those disorders were found in 68% and 42% of dyspeptic patients with or without delayed GE, respectively (Triadafilopoulos et al., 2017). These associations suggest overlapping gastric and oesophageal neuromuscular alterations in their pathophysiology.

Colonic diseases

The interplay between both inflammatory bowel diseases (IBD) and diverticular disease will be detailed in the paragraph “From colon to stomach” (see 1.7. Cross-organ sensitisation between the upper and lower gastrointestinal tracts: state of the art).

Overlaps with other disorders of gut-brain interactions

Overlaps between different DGBI are common: among individuals meeting the criteria of one or more of the GORD, FD and IBS conditions, 30.7% had an overlap between two or all three conditions (Rasmussen et al., 2015). In particular, FD frequently overlaps with other DGBI, especially GORD or IBS, found in 24 and 14% of Rome II-based dyspeptic subjects, respectively, in a Korean study

(Lee et al., 2009). In a cross-sectional study of Japanese workers, overlaps with GORD and/or IBS were found in 47.6% of patients with FD (Kaji et al., 2010).

These overlaps seem to occur predominantly in anxious people, and anxiety is significantly associated with overlap with GORD and IBS in FD (OR 3.19 [95% CI: 1.33-7.63]) compared with FD alone in the Korean population (Lee et al., 2009).

There is no data on the overlap with functional chest pain, globus, functional dysphagia, functional abdominal bloating with or without distension, and functional anorectal disorders in FD. The presence of rumination syndrome or dysphagia is an exclusion criterion in trials concerning FD (Carbone et al., 2016).

The disorders are classified by anatomic regions according to the presumed organ involved in symptom generation.

Oesophageal disorders

Gastro-oesophageal reflux (GOR) is the phenomenon of retrograde movement of gastric contents into the oesophagus, which can happen in healthy subjects. The primary mechanism underlying GOR is the advent of transient lower oesophageal sphincter relaxations (TLESRs). Gastric distention triggers the appearance of TLESRs, probably through the activation of mechanoreceptors in the stomach, since there is a negative correlation between the change in IGP in response to a meal (i.e. fundic accommodation) and the number of TLESRs in both healthy volunteers and patients with GORD (Pauwels et al., 2014). **Gastro-oesophageal reflux disease** is defined as abnormal oesophageal acid exposure together with pathologic symptom association probability on pH/impedance monitoring. The disease has different phenotypic presentations: non-erosive reflux disease (NERD) in the absence of endoscopic features, erosive oesophagitis if mucosal breaks are identified at endoscopy, Barrett's oesophagus, and peptic stricture (Gyawali et al., 2018). It can be diagnosed by a clinician's symptom assessment, using a questionnaire, by endoscopy or more rigorously by physiological testing (24-hour oesophageal pH monitoring or multichannel intraluminal impedance-pH testing (MII-pH)), among other things. Typical symptoms of GORD are heartburn and acid regurgitation (Vakil et al., 2006). Patients with symptoms of heartburn can also have other disorders, especially functional oesophageal disorders in which oesophageal mucosa is normal: **reflux hypersensitivity**, if symptoms are triggered by reflux events (positive symptom

association probability) but with normal acid exposure, and **functional heartburn**, if the symptom is reported in the absence of GORD, reflux hypersensitivity and response to PPI therapy (Aziz et al., 2016). A diagnosis of FD according to Rome criteria requires a normal upper GI endoscopy; therefore, the prevalence of erosive reflux disease is null by definition in patients with FD. However, there is considerable overlap between FD and GORD symptoms, with 31.3% (95% CI: 19.4-46.3) of subjects with FD complaining of heartburn and/or acid regurgitation in a recent meta-analysis (Geeraerts et al., 2020). Similarly, in a population-based study, overlapping reflux symptoms were present in 33.8% of subjects with dyspeptic symptoms (Piessevaux et al., 2009). Pleyer et al. found evidence supporting a systematic bias favouring a GORD diagnosis over FD (Pleyer et al., 2014). The proper assessment of GORD in patients with FD, defined by pH monitoring, was only performed in a few studies. Abnormal acid exposure on pH monitoring was found in 23.5% of patients with FD without dominant heartburn (Tack et al., 2005). In another study, abnormal acidic reflux affected 22.8% of FD patients (Melashchenko et al., 2019). Delayed GE is associated with more GOR events but does not affect oesophageal acid exposure (Gourcerol et al., 2013). In particular, 43.2% of dyspeptic patients with delayed GE had abnormal oesophageal acid exposure, in contrast to 37.5% of those with normal GE ($p > 0.05$) (Triadafilopoulos et al., 2017). On the other hand, duodenal eosinophilia was associated with an increased risk of developing GORD in FD patients (OR 4.2 [95% CI: 1.2-4.77] after ten years) (Ronkainen et al., 2019).

Gastro-duodenal disorders

Belching is the noisy gas emission from the oesophagus or stomach through the mouth. Intraluminal impedance measurements can distinguish supra-gastric and gastric belching, the two **belching disorders**. Aerophagy, a historical term focussing on swallowing air, has been reported in 27.6% of FD patients (Talley et al., 1986). Increased non-acid gaseous GOR has been reported in FD patients (Conchillo et al., 2007). Patients with FD, recruited from a population consulting for a health check-up, have clinically significant belching in 14.4% of cases (Fujiwara et al., 2021).

Nausea and vomiting have numerous causes. In the absence of an aetiological factor, they are considered of unexplained origin and to be functional (Stanghellini et al., 2016). **Chronic nausea and vomiting syndrome** was reported

in 82.4% of patients with symptoms of gastroparesis (Jehangir and Parkman, 2018). **Cyclic vomiting syndrome** was reported by 6.9% and **rumination syndrome** by 3.4% of FD patients in a Japanese secondary care setting (Nakajima et al., 2010). An overlap with rumination syndrome is present in 16.0% (95% CI: 11.1-21.9) of FD patients, which is 3.8 times more likely than expected by chance (Zand Irani et al., 2021). Rumination syndrome is likely underdiagnosed in clinical practice, with a global prevalence of 3.1% (95% CI: 3.0-3.3) (Josefsson et al., 2022a).

Bowel disorders

The overlap with **irritable bowel syndrome**, a lower GI disorder characterised by abdominal pain or discomfort associated with altered bowel habits without an organic cause for the symptoms, is the most commonly reported comorbidity in FD (Agr us et al., 1995, Caballero-Plasencia et al., 1999).

The studies which assessed the prevalence of the FD-IBS overlap in the general population found values of 0.9% (Kaji et al., 2010) to 5% (Wang et al., 2008a). Based on Rome IV criteria, the prevalence of overlapping FD-IBS was 11.7% in an internet-based survey in Bulgaria (Nakov et al., 2020). A Japanese study from the general population even found a prevalence of FD-IBS overlap in 23-24% of the subjects questioned (Hongo, 2011). Overlap between FD and IBS in the general population, however, lacks stability over time, with approximately 50% of the patients changing their symptom profile over one year (Agr us et al., 1995). A meta-analysis showed that the prevalence of IBS among subjects with FD was 37% (95% CI: 30-45), compared to 7% (95% CI: 5-10, $p < 0.001$) among those without, with an OR of 8.00 (95% CI: 5.74-11.16) (Ford et al., 2010a). Community-based surveys in Spain and Bangladesh found 31.6 and 42.1% of subjects with FD to have IBS (Caballero-Plasencia et al., 1999, Perveen et al., 2014).

Studies involving patients from gastroenterology outpatient clinics in secondary and tertiary care have gone further in investigating FD-IBS overlap. The only independent risk factor associated with FD-IBS overlap vs FD alone was the presence of postprandial fullness (Wang et al., 2008a). Patients with overlapping FD-IBS do not have more delayed GE or abnormal fundic accommodation following a meal than those with FD alone (Corsetti et al., 2004). Still, they have a greater prevalence of hypersensitivity to gastric distension (44.0 vs 28.0%, $p = 0.02$) (Corsetti et al., 2004), which usually occurs in a subset of FD patients (Tack

et al., 2001). The overlap between FD and IBS is consistently associated with decreased QoL, higher dyspeptic severity scores, altered sleep and higher depression scores (Wang et al., 2008a, Kaji et al., 2010, Futagami et al., 2013b). Overlapping FD-IBS is associated with increased symptom severity of both IBS and FD in those patients (von Wulffen et al., 2019). Patients with FD-IBS overlap are more frequently women, and have more significant weight loss (Corsetti et al., 2004). Women suffering from overlapping FD-IBS experience more severe GI symptoms and depression levels than men (Nam et al., 2021).

Risk factors associated with FD-IBS overlap in the general population are gender, milk intolerance, and urinary and sexual problems (Nakov et al., 2020). Marital status (single, divorced or widowed), symptoms of nausea and bloating, and a feeling of incomplete emptying after bowel movements were independent risk factors for FD-IBS overlap among IBS patients, and young age, depression, bloating, and the PDS subtype were associated with this overlap among FD patients in another study (Choi et al., 2017). Factors associated with overlapping FD-IBS in Japanese workers were female gender (OR 1.72 [95% CI: 1.03-2.85]) and cigarette smoking (OR 2.26 [95% CI: 1.40-3.66]), while lower BMI was protective (OR 0.54 [95% CI: 0.34-0.87]) (Fujiwara et al., 2011).

Functional diarrhoea and functional constipation are considered a continuum with IBS among functional bowel disorders, IBS being distinguished by a more present painful component (Lacy et al., 2016). Physiologically, voluntary suppression of defaecation delays GE in healthy subjects (Tjeerdsma et al., 1993). A third of patients with symptoms of gastroparesis (88.2% of whom met Rome III criteria for FD) experienced severe **constipation** or delayed colonic transit (Parkman et al., 2022a). In this study, the severity of constipation was associated with dyspeptic symptoms severity, the overlap with IBS, and delayed small bowel and colonic transit times, but not with delayed GE (Parkman et al., 2022a). Patients with gastroparesis had a higher prevalence of slow transit constipation, diagnosed by a radiopaque marker study, than those with normal emptying (64.7 vs 28.1%, $p = 0.013$) (Zikos et al., 2019).

Gallbladder and sphincter of Oddi disorders

Motor disorders of the gallbladder (functional gallbladder disorder) and the sphincter of Oddi (functional biliary sphincter dysfunction) are thought to explain biliary pain in some patients (Cotton et al., 2016). Patients with **sphincter**

of Oddi dysfunction had or developed FD in 41% and 14% of the cases in endoscopic sphincterotomy and non-endoscopic sphincterotomy groups, respectively (Miyatani et al., 2019).

Anorectal disorders

Functional anorectal disorders include faecal incontinence, functional anorectal pain, and functional defaecation disorders (Rao et al., 2016). No data in FD patients is available.

Overlaps with non-gastrointestinal functional somatic disorders

Several chronic pain states have been associated with DGBI, as shown in Figure 1.3. A heterogeneous nomenclature has been used in the literature to group all those disorders: "somatoform disorders", "functional pain syndromes", "functional somatic syndromes", etc. (Petersen et al., 2020). The current trend is to gather somatic and visceral pain syndromes into the concept of "central sensitivity syndromes" (Yunus, 2007), a group of inter-related disorders without organic abnormalities that are likely to explain their symptoms and characterised by central sensitisation (Woolf, 2011). This group includes the following conditions (non-exhaustive list): IBS, migraine, tension headaches, CFS, multiple chemical sensitivity syndrome, temporomandibular joint disorder, fibromyalgia, chronic pelvic pain syndrome, BPS, myofascial pain syndrome, mechanical low back pain, whiplash-associated disorders, restless leg syndrome, post-traumatic stress disorder (PTSD, discussed in the chapter about psychiatric conditions), and so on. Vulvodynia and premenstrual tension syndrome are also frequently associated with this spectrum; however, no central sensitisation has been proven in those disorders. Apart from fibromyalgia and CFS, some syndromes in this category are also defined by environmental exposures, like the Gulf War syndrome (affecting military veterans of the 1990-1991 Persian Gulf War and distinct from PTSD) and the Sick Building Syndrome (affecting some building occupants experiencing health effects in relation to the time spent in a building), and others are organ-specific (migraine or BPS, for example). All those pain disorders will be called non-GI functional somatic disorders in this work (Burton et al., 2020).

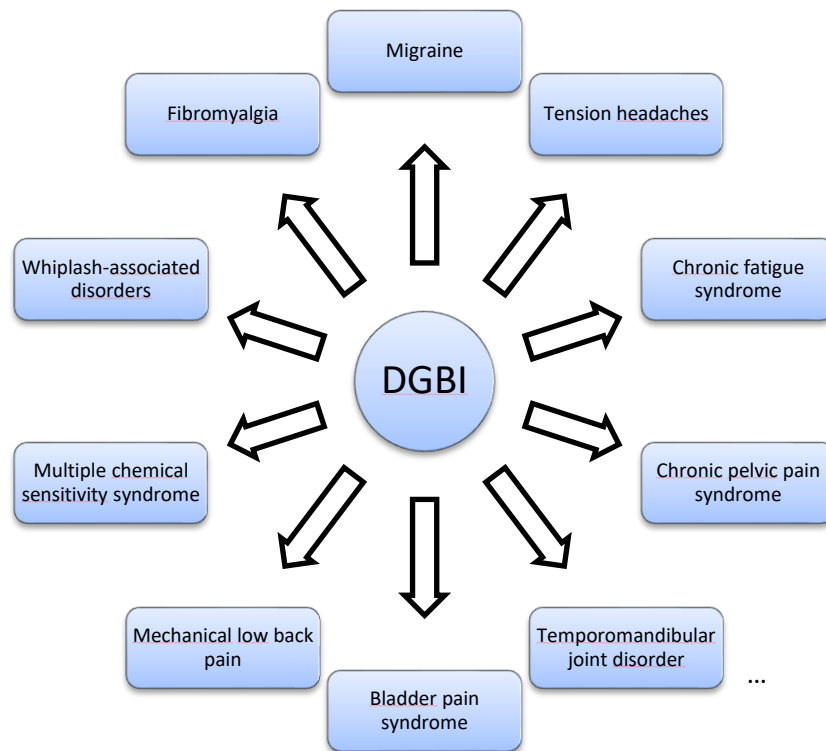


Figure 1.3. The spectrum of functional somatic syndromes possibly associated with disorders of gut-brain interactions.

DGBI: disorders of gut-brain interactions.

Fibromyalgia syndrome

Fibromyalgia is a syndrome characterised by chronic and widespread musculoskeletal pain associated with non-painful manifestations (fatigue, sleep alterations, etc.). Dyspepsia is reported in 48.6% of patients diagnosed with fibromyalgia syndrome (Yim et al., 2017). Functional dyspepsia, according to Rome II criteria, was present in 21% (95% CI: 13-29) of fibromyalgia patients compared to 3% (95% CI: 0-6.3, $p < 0.001$) of healthy subjects among the Spanish population (Almansa et al., 2009). However, according to a recent systematic review, no data is available about the prevalence of fibromyalgia in a population of FD patients (Erdrich et al., 2020).

Chronic fatigue syndrome

Chronic fatigue syndrome is a disease defined by extreme fatigue lasting for more than six months and which cannot be explained by an underlying disorder (including depression). The condition was also named “myalgic encephalomyelitis” (ME), “ME/CFS”, or “post-viral fatigue syndrome”, among others. It is considered a viral-onset illness. Chronic fatigue-like symptoms were found in 39.4% of tertiary care patients with FD, with risk factors being depression and somatisation (Van Oudenhove et al., 2011c). General fatigue was reported in 95.3% of FD patients (Gracie et al., 2015).

Headaches

Headaches, in general, have been reported in 10.6% of FD patients (Brook et al., 2012).

Tension-type headaches, the most common type, are diffuse mild-moderate headaches described as pressure around the head. No data is available about their prevalence in patients with FD, however, one study reported a prevalence of 22.2% in patients with refractory FD (Shahbazkhani et al., 2020).

Recurrent attacks of moderate-severe headaches characterise **migraine**. Updated criteria for migraine diagnosis have been available since 2018, with the third edition of the International Classification of Headache Disorders (ICHD-3) (Headache Classification Subcommittee of the International Headache Society, 2018). Migraine headaches have been reported in 54% of patients with EPS and 76% of those with PDS in a cohort study of 60 patients with FD (Di Stefano et al., 2019). The prevalence of migraine was 42.8% among FD patients in a population-based survey concerning Olmsted County in the USA (Zand Irani et al., 2021). Migraine onset was meal-unrelated in all patients with EPS and meal-related in 89% of those with PDS in this study (Di Stefano et al., 2019). Migraine was reported 1.7 times more frequently by dyspeptic patients than by those without dyspepsia (OR 1.68 [95% CI: 1.23-2.29]) in a population-based study in Iran (Lankarani et al., 2017).

Functional urological disorders

Overactive bladder and BPS are two functional urological disorders, which are easily confused due to the wide overlap of symptoms and the frequent association between the two conditions, as shown in Figure 1.4.

Overactive bladder is defined by urinary urgency, with or without incontinence. The disorder was found in 20.5% of patients with FD (OR 2.85 [95% CI: 2.21-3.67]) in a web survey (Matsuzaki et al., 2012), whereas FD was found in 7.2% of patients with overactive bladder (Persson et al., 2015).

Interstitial cystitis/bladder pain syndrome (IC/BPS), or **bladder pain syndrome** in simplified form, formerly known as interstitial cystitis or interstitial cystitis/painful bladder syndrome (IC/PBS), is defined by chronic pelvic pain associated with lower urinary tract symptoms. The diagnosis can be based on the criteria of the European Society for the Study of Interstitial Cystitis (ESSIC criteria, see Table 8.1) (van de Merwe et al., 2008). The disorder was found in 3.7% of the general population (Ibrahim et al., 2007). Its aetiology is unknown. The condition is categorised according to the presence or not of Hunner lesions at cystoscopy; indeed, the subtype with Hunner lesions is a distinct inflammatory disease (Whitmore et al., 2019). The workup includes history, physical examination and urinalysis. Cystoscopy is only indicated when the diagnosis is doubtful or when Hunner lesions are suspected. The management strategies have recently been updated (Clemens et al., 2022). Treatment options include behavioural modifications, oral medications (painkillers, neuromodulators, etc.) and low-pressure hydrodistension, among others. Dyspeptic symptoms are frequently reported by patients suffering from BPS (Chelimsky et al., 2012).



Figure 1.4. Continuum between overactive bladder (OAB) and bladder pain syndrome (BPS).

Chronic genito-pelvic pain and sexual function

Chronic pelvic pain syndrome (CPPS), previously termed chronic prostatitis and chronic prostatitis/chronic pelvic pain syndrome, is a chronic (> six months) pain condition located in the pelvic region, limiting daily functioning, and without an underlying organic disease (unrelated to menses, pregnancy and

previous pelvic surgery; endometriosis excluded in women) (Rees et al., 2015). No data in FD patients is available.

Chronic vulvar pain is classified in vestibulodynia and vulvodynia (Bornstein et al., 2016). In Italy, chronic vulvar pain is due to **provoked vestibulodynia** in three-quarters of the cases and **vulvodynia** in one-quarter (Graziottin et al., 2020). No data in FD patients is available.

Any **menstrual pain** was associated with FD in female Japanese university students compared to those without FD (91.3 vs 83.3% respectively, $p < 0.001$). Heavy menstrual pain was also associated with FD in this cross-sectional study (27.8 vs 14.6%, respectively, $p < 0.001$). The association was only present with the PDS subtype and not the EPS subtype. Heavy menstrual pain was independently associated with FD (OR 3.18 [95% CI: 1.60-6.89]) (Yamamoto et al., 2022).

Sexual disorders include disorders of desire and arousal. In a case-control study, **sexual dysfunction** was present in 42.3% of FD patients, compared to 16.1% of healthy controls (Fass et al., 1998). A decreased sexual drive was reported by 15.7% of FD patients compared to 7.3% of controls, whereas **dyspareunia** was rarely observed in FD patients (Fass et al., 1998). In a population-based study, “sexual problems” were reported by 34.0% of FD patients in comparison with 21.1% of those without FD ($p < 0.001$) (Nakov et al., 2020).

Chronic low back pain

Chronic mechanical low back pain is widespread in the general population, with a global prevalence of 7.50% (Wu et al., 2020). It was reported in 3.3% of FD patients in a population-based cohort (Garcia-Etxebarria et al., 2022) but in 80.8% of them in secondary care (Gracie et al., 2015).

Disorders of orthostatic intolerance

Orthostatic intolerance is defined by symptoms appearing in an upright position and being relieved by a supine position (Gutkin and Stewart, 2016). Disorders of orthostatic intolerance include orthostatic hypotension, postural vaso-vagal syncope and postural tachycardia syndrome (POTS).

Postural orthostatic tachycardia syndrome is characterised by an increase in heart rate ≥ 30 beats per minute upon standing associated with symptoms of brain hypoperfusion and increased sympathetic activity (Freeman et al., 2011, Narasimhan et al., 2022). There is frequently a viral onset and the

disorder is often associated with symptoms independent of the autonomic nervous system (ANS) and with other non-GI functional somatic syndromes. No data in FD patients is available.

Multiple chemical sensitivity

Multiple chemical sensitivity is a disorder characterised by an overreaction, with the triggering of various symptoms, following the exposure to odours or chemical products (metals, solvents, pesticides, etc.) below toxic ranges for the general population, without an allergic substrate and after excluding organic diseases, porphyria or mastocytosis in particular. The prevalence of self-reported diagnosis in the German population is 9%, whereas it is 0.5-6.5% in medically evaluated patients (Hausteiner et al., 2005, Pigatto and Guzzi, 2019). The condition can be screened using the 3-item Brief Environmental Exposure and Sensitivity Inventory (BREESI) questionnaire (Palmer et al., 2020), with possible patients undergoing the complete evaluation by the Quick Environmental Exposure and Sensitivity Inventory (QEESI®) (Miller and Prihoda, 1999, Hojo et al., 2003). Gastrointestinal manifestations include heartburn, food intolerances, IBS symptoms, etc. The treatment is challenging and mainly relies on evicting incriminated substances (Damiani et al., 2021). No data in FD patients is available.

Temporomandibular disorders

Temporomandibular disorders (TMD) is the umbrella term for many clinical signs and symptoms of the structures of the masticatory system. Diagnostic criteria involve diagnostic algorithms (Axis I) and screening instruments (Axis II) (Schiffman et al., 2014). The taxonomy of TMD includes 37 disorders, mainly **temporomandibular joint disorders** and **masticatory muscle disorders** (Peck et al., 2014). No data in FD patients is available.

Sleep bruxism

Bruxism is a sleep disorder characterised by grinding noises during sleep. It was commonly assumed that bruxism was one of the main risk factors for temporomandibular disorders until recently. Even if patients with TMD self-reported sleep bruxism more frequently than controls, similar rates were found in both groups when using objective assessment of the condition during

polysomnography, however (Raphael et al., 2012). No data in FD patients is available.

Restless leg syndrome

Restless leg syndrome is a sleep-related movement disorder, characterised by an irrepressible urge to move the legs during sleep, with a prevalence of 3.0% (95% CI: 1.4-3.8%) (Brostrom et al., 2023). No data in FD patients is available.

Other pain disorders

Myofascial pain (dysfunction) syndrome is a disorder characterised by chronic pain arising from muscles, fascia and soft tissues in the absence of fibromyalgia, CFS, polymyalgia rheumatica, and polymyositis, and associated with myofascial trigger points and fascial contractions (Cao et al., 2021). No data in FD patients is available.

Complex regional pain syndrome is a chronic condition characterised by continuing regional pain that develops after an injury or surgery and typically affects a limb (Goebel et al., 2021). No data in FD patients is available.

A **whiplash-associated disorder** is defined by chronic neck pain following an injury with acceleration-deceleration applied to the cervical spine, typically after a motor vehicle crash, with central sensitisation involved in the chronicisation of pain (Van Oosterwijck et al., 2013). No data in FD patients is available.

Overlaps with psychological factors and psychiatric conditions

All psychological attributes have state and trait components: a state is a temporary way of being, while a trait is more stable and related to personality features. For example, *state anxiety* is a transient emotional response to a stressful situation, while *trait anxiety* is a constant response to any problem worryingly.

Associations with psychosocial factors are classically found in FD, including psychological distress (anxiety and depression), somatisation (Wilhelmsen et al., 1995), sleep alterations, and so on. Psychological factors (depression, abuse

history and somatisation) are major determinants of the severity of symptoms in FD (Van Oudenhove et al., 2008).

The role of a history of abuse is classically described in IBS patients. A history of abuse is associated with increased GI and non-GI symptom severity in those patients (Melchior et al., 2022b). Only sexual abuse in childhood and physical abuse in adulthood directly affected non-GI symptom severity, with other associations being mediated by GI-specific anxiety, depressive symptoms and visceral hypersensitivity in this study (Melchior et al., 2022b). Patients with sexual abuse in childhood also have a lower discomfort threshold during gastric distension (Geeraerts et al., 2009). Childhood abuse was also directly associated with neuroticism, which initiates a "vicious circle" of mood disorders and pain/bowel symptoms (Jones et al., 2013b). A history of childhood abuse was associated with the development of FD (Oshima et al., 2015). Adulthood abuse was not more frequent in FD patients compared to healthy subjects (41.7 vs 25.6%, $p = 0.080$), nor was it an independent predictor of FD when other psychological factors were controlled for in the analyses (Koloski et al., 2005b).

Anxiety disorders

Patients with FD have a two-fold increased risk of a **generalised anxiety disorder** (OR 2.03 [95% CI: 1.06-3.89], $p < 0.001$), a condition characterised by excessive worrying (Mak et al., 2012). In a Swedish population-based study, anxiety was associated with FD and PDS, but not EPS (Aro et al., 2009). Acute anxiety and anxiety disorders were also associated with impaired gastric accommodation in FD (Ly et al., 2015). Anxiety, but not depression, increases the risk of developing FD by 7.6 times (OR 7.61 [99% CI: 1.21-47.73]) in the following ten years (Aro et al., 2015). Anxiety traits have been associated with healthcare-seeking behaviour in FD (Hu et al., 2002).

Lifetime **agoraphobia**, defined as a "disproportionate fear of public places" in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (American Psychiatric Association, 2013), was reported in 22% of women with FD in a small cohort study (Malt et al., 2000), while **panic disorder**, characterised by recurrent panic attacks, was not associated with the disorder.

Thymic disorders

Mood (affective) disorders include **depression** and bipolar disorder. Major depressive disorder is characterised by more than two weeks of sadness and a lack of interest or pleasure in activities. There is a positive association between FD and depression, with an OR of 2.28 (95% CI: 2.02-3.81), and patients from Europe seemed to be more likely to have depression compared with those from Asia (OR 6.19 vs 2.47) in a recent meta-analysis (Lin et al., 2019). This is concordant with a community-based study which found patients with FD to be at a three-fold increased risk of a major depressive episode (OR 3.56 [95% CI: 2.33-5.43]) (Mak et al., 2012). The lifetime incidence of mood disorders was estimated at 83% in a small cohort study involving only women with FD (Malt et al., 2000).

Sleep disorders

Sleep disorders are common in the general population, with 27% reporting trouble staying asleep in a community-based survey (Cremonini et al., 2009). The taxonomy of sleep disorders in the International Classification of Sleep Disorders-third edition (ICSD-3) includes 83 conditions divided into seven main categories: insomnia disorders, sleep-related breathing disorders, central disorders of hypersomnolence, circadian rhythm sleep-wake disorders, sleep-related movement disorders, parasomnias, and others (Sateia, 2014).

Functional dyspepsia is associated with sleep disorders in half to more than two-thirds of the cases (Fass et al., 2000, Lu et al., 2005, Lacy et al., 2011, Futagami et al., 2013a, Shimpuku et al., 2014, Li et al., 2018, Andreev et al., 2021).

Somatisation

Somatisation is the inclination to experience somatic symptoms in response to psychosocial stress and to seek medical help for it (Lipowski, 1986). Somatic symptom disorder, previously known as somatisation disorder, is characterised by complaints of somatic symptoms without an organic aetiology and is recognised as a psychiatric disease in the DSM-5 (American Psychiatric Association, 2013). Greater somatisation scores and an increased number of somatic symptoms were found in FD patients compared to subjects from the general population without dyspepsia (Aziz et al., 2018a), where they were similar in FD patients compared to those suffering from organic dyspepsia in secondary care cohort (Gracie et al., 2015). Somatisation is a major determinant of the

symptom severity in FD (Van Oudenhove et al., 2008). Somatisation can be assessed in patients using validated scores, detailed in the methodological chapter (see 4.2. Assessment of symptom burden in disorders of gut-brain interactions).

Stress & stressful life events

Psychosocial stress and coping style were shown to predict FD in a small case-control study (De la Roca-Chiapas et al., 2010). Childhood abuse is directly associated with neuroticism and initiates a "vicious circle" of mood disorders and pain/bowel symptoms (Jones et al., 2013b). A history of childhood abuse was associated with the development of FD (Oshima et al., 2015).

Eating disorders

Eating disorders are psychiatric disorders characterised by abnormal eating habits. They include **anorexia nervosa**, **bulimia nervosa**, **binge eating disorder**, **avoidant/restrictive food intake disorder** (ARFID), and **eating disorders not otherwise specified**. "Extreme picky eating", another name for ARFID, is a newly described eating disorder characterised by the inability to eat certain foods based on smell, texture, colour, and so on. According to an Italian study, the majority (83.3-90%) of patients with eating disorders fulfil the criteria for PDS (Santonicola et al., 2012). A systematic review confirmed that DGBI, such as IBS and FD, are frequent comorbidities in patients with eating disorders (Hanel et al., 2021). Another study found that 39.9% of patients presenting gastroparesis/dyspepsia symptoms meet the criteria for ARFID (Burton Murray et al., 2020). Clinicians should therefore be cautious about the presence of an eating disorder in patients with FD, especially in the subgroup of PDS (Murray et al., 2021).

Post-traumatic stress disorder

Post-traumatic stress disorder (PTSD) is a psychiatric disorder in which patients have negative thoughts or feelings which develop after exposure to a traumatic or stressful event, the subject persistently re-experiencing it (American Psychiatric Association, 2013). Women veterans with dyspepsia were found to have PTSD in 25.5% of the cases; the prevalence is higher than in those without dyspepsia (Savas et al., 2009).

Personality traits

Personality (dissociative) disorders were previously named multiple personality disorder. Apart from this psychiatric disease, different personality traits are described. Higher scores of **neuroticism**, a personality trait in which one experiences the world as threatening, were also associated with an increased risk of FD in the general population (OR 1.04 [95% CI: 1.03 - 1.06]) (Sharbafchi et al., 2020). Higher scores of **perfectionism**, particularly parental criticism, are also found in FD patients compared to controls (Ochi et al., 2008). **Alexithymia** is a condition in which subjects have difficulties in identifying feelings and describing emotions. Patients with FD had modestly higher scores on measures of alexithymia in one study (Jones et al., 2004). **Hypervigilance** to abdominal events, assessed through GI-specific anxiety, was correlated with symptoms of epigastric pain/discomfort and fullness in a fasting state in FD patients (Steinsvik et al., 2020). **Catastrophising** is the tendency for a person to exaggerate a difficulty and to believe that the worse situation will occur. A lack of emotion regulation can lead to pain catastrophisation; patients with chronic pain conditions and catastrophisation are probably those who will benefit the most from psychological therapies.

The association of FD with different comorbidities raises the question of the mechanisms involved in these overlaps, which will be the subject of the following subchapter.

1.3. Pathophysiology of overlaps in functional dyspepsia

The pathophysiology of DGBI is multifactorial, with alterations in the gut-brain axis considered a central factor. Other important factors in the pathophysiology of these disorders include micro-inflammation with immune dysregulation (e.g. mast cells in contact with sensitive nerve endings in the digestive wall) and psychological factors, among others. Risk factors include female gender, infections, and adverse life events. The mechanisms of overlaps between different DGBI and a DBGI and a non-GI disorder must be better understood. However, different mechanisms have been described or can be

suspected to explain overlaps between FD and another DGBI or diseases not belonging to DGBI.

Common causal factors, especially stressful life events and infections, could explain the frequent overlap between different DGBI. A post-infectious origin has also been described for different DGBI. Acute *Salmonella*, *Shigella* and *Campylobacter* gastroenterites are recognised as a cause of IBS, with the most potent risk factor for developing post-infectious IBS (PI-IBS) being female sex (RR = 2.2 at six years) (Neal et al., 2002). More recently, an outbreak of *Salmonella* gastroenteritis in 2002 in a Spanish village showed that it was a risk factor for developing IBS but also FD, with a relative risk of 5.1 at one year (Mearin et al., 2005). While subjects who developed FD alone recovered gradually over time, those with FD-IBS overlap remained stable. Overlaps between DGBI are particularly common in this particular population, with, for instance, 68.2% of overlaps between IBS and FD one year following an epidemic of water-borne giardiasis that broke out in Norway in 2004 (Dizdar et al., 2007). Sporadic acute infectious diarrhoea in tropical countries, including *Vibrio cholerae* infection, is sometimes followed by post-infectious DGBI (Rahman et al., 2018). A PI-FD could also be associated with developing other conditions of post-infectious origin over time. Indeed, the prevalences of FD, IBS, overactive bladder and chronic fatigue six years after an outbreak of *Giardia* infection were all superior in exposed compared to non-exposed subjects (21.0 vs 6.6%, 40.1 vs 11.9%, 18.7 vs 13.6%, and 31.6 vs 11.4%, respectively, with p-values [p] < 0.01 for all) (Persson et al., 2015).

Genetic factors are probably also involved, as evidenced by the fact that monozygotic twins are more likely to be concordant than dizygotic twins for IBS. A twin study has shown a genetic contribution to GORD and IBS (potentially mediated by the heritability of anxiety and depression), but not to FD (Lembo et al., 2007). In IBS, the genetic contribution seems particularly important for women (Bengtson et al., 2006). A genetic basis for extra-intestinal symptoms in IBS has been found in a population-based sample of twins (concordance rates of 30.0% and 16.7% in monozygotic and dizygotic twins, respectively, p = 0.02) (Lembo et al., 2009). For instance, the long allele (L/L) genotype of 5-HTTLPR (serotonin-transporter-linked promoter region) was a risk factor for the overlap with constipation-predominant IBS in FD patients in South Korea (OR 12.47 [95% CI: 2.00–77.75]) (Choi et al., 2017). Similarly, common pleiotropic genetic

determinants of gut diseases, like IBS or GORD, and psychiatric disorders, like major depressive disorder or PTSD, support the core role of the gut-brain axis in the pathophysiology of DGBI and could explain in part the frequency of their overlaps (Gong et al., 2023).

Shared pathogeneses between different disorders could explain some overlaps. For instance, altered GI motility, visceral hypersensitivity and/or low-grade inflammation in different segments of the GI tract could be involved in overlapping DGBI. Similarly, the association between FD and oesophageal motility disorders suggests overlapping gastric and oesophageal neuromuscular alterations in their pathophysiology (Triadafilopoulos et al., 2017).

The **physiological interplay** between different segments of the GI tract could also be involved in the overlap between FD and another DGBI. Indeed, a DGBI affecting one part of the GI tract could alter the sensorimotor function in a remote part via prevertebral neural reflex pathways and/or altered gut peptide release. For example, slow transit constipation is associated with impaired gastric accommodation (Penning et al., 2001) and impaired fundic accommodation triggers TLESRs, leading to GOR events (Pauwels et al., 2014).

The development of different DGBI and non-GI functional disorders in the same patients following an infection suggests a role for **systemic inflammation** in the pathophysiology of these overlaps. The passage of lipopolysaccharide (LPS), a component of the wall of Gram-negative bacteria, into the blood induces fever and sickness behaviour, among other things. Acute experimental endotoxemia (intravenous injection of LPS) induces colorectal hypersensitivity in healthy subjects (Benson et al., 2012), proving an interplay between gut nociception and systemic **immune activation**. For example, increased circulating $\alpha 4 \beta 7^{+}$ gut-homing T cells are described in both FD and IBS (Burns et al., 2019). Immune activation could also explain the associations with autoimmune diseases or allergic conditions.

Gastrointestinal micro-inflammation could also be involved. Duodenal eosinophilia in the second portion of the duodenum was independently associated with an increased risk of GORD after ten years of follow-up in FD patients (OR 4.2 [95% CI: 1.2-4.77]) and even more in patients with PDS (OR 6.0 [95% CI: 1.50-23.6]), in the Kalixanda study (Ronkainen et al., 2019). However, duodenal mast cell hyperplasia, but not duodenal eosinophilia, was linked to IBS (Walker et al., 2009). Gut micro-inflammation is also a trigger for new-onset

disorders outside the GI tract. For instance, duodenal eosinophilia is a hallmark of FD (Shah et al., 2022) but increased eosinophils in the first portion of the duodenum were also associated with new-onset anxiety in the general population (Ronkainen et al., 2021).

Increased gut permeability, also known as “leaky gut”, could also play a role. Indeed, a cause-and-effect relationship between increased gut permeability and the development of visceral hypersensitivity has been suggested in a stress model involving female Wistar rats, where preventing the mucosal barrier alterations was accompanied by a decrease in sensitivity to colorectal distension (CRD) (Ait-Belgnaoui et al., 2005). The links between duodenal immune activation, dysbiosis and barrier dysfunction in FD is an ongoing field of research (Hari et al., 2022).

Psycho-social and cognitive factors (fatigue, sleep, anxiety, depression, social stigma, concentration, memory, etc.) affecting the entire digestive tract may be a causal factor in the pathogenesis of the overlaps between FD and another DGBI. For example, veterans with an FD-IBS overlap have higher scores for anxiety, depression, and PTSD (Savas et al., 2009). Those factors are also classically altered in other chronic pain conditions (Adams and Turk, 2015). For example, depression is a risk factor for complaining of chronic fatigue-like symptoms in FD patients (Van Oudenhove et al., 2011c).

Different forms of **stress**, particularly early in life, such as physical trauma, loss of a parent, and physical/sexual abuse, are all associated with an increased risk of developing DGBI later in life (Chitkara et al., 2008). Acute stressors, such as sexual abuse, a near-fatal traumatic event, and warfare, are also risk factors for developing IBS (Irwin et al., 1996). It is also known that the most predictive factors for developing PI-IBS are stress (represented by a recent traumatic life event) and a neurotic personality trait (Gwee et al., 1996). Women who report domestic violence to the police frequently suffer from a DGBI: 67% have FD, 47% IBS and 43% FD+IBS overlap, with onset occurring simultaneously or soon after the start of abuse in two-thirds of the cases (Perona et al., 2005).

Somatisation is the psychological mechanism by which a subject expresses psychological distress through physical symptoms. Somatic symptoms due to somatisation can be viewed as a psychological defence against mental instability, converting psychological pain into physical pain. Without reaching the stage of disease, somatisation can therefore be seen as a measure of

psychological health. This process is distinct from malingering and factitious disorder, where the patient consciously decides to fake illness, the underlying motivation being conscious in the former case and unconscious in the latter. Patients with somatisation report numerous symptoms (Wessely et al., 1999). Somatisation is a risk factor for overlapping DGBI in the population (Choung et al., 2017). The number of different anatomical regions of overlapping DGBI increases in parallel to somatisation (Sperber et al., 2022). Depression and somatisation levels are associated with increased postprandial symptoms in IBS patients (Van Oudenhove et al., 2016c). Somatisation also seems implicated in the overlap with non-GI disorders. Indeed, it is a risk factor for complaining of chronic fatigue-like symptoms in FD patients, for example (Van Oudenhove et al., 2011c). Methods to assess somatisation are detailed elsewhere (see 4.2. Assessment of symptom burden in disorders of gut-brain interactions).

Mixed symptomatology, with the non-GI disease causing dyspeptic symptoms or FD causing symptoms in other organs, could also explain some overlaps. For example, signs of early chronic pancreatitis were found in about one-quarter of PPI-resistant FD patients in a Japanese study (Wakabayashi et al., 2018). Patients with eating disorders also frequently fulfil symptom-based criteria for PDS (Hanel et al., 2021). Furthermore, Rome diagnostic criteria separate different DGBI arbitrarily by anatomical regions, which could explain some overlap between FD and another DGBI.

Medications used to treat the non-GI disorder could cause dyspeptic symptoms, or those used to treat FD could cause symptoms in other organs. For example, drugs classically known to induce dyspeptic complaints include NSAIDs (Yap and Goh, 2015), opioids, metformin, etc.

Visceral hypersensitivity could also explain, at least in part, the existence of overlaps between DGBI. In particular, gastric hypersensitivity is more common in FD patients with overlap with IBS compared to those with dyspepsia alone (44.0 vs 28.0%, $p = 0.02$) (Corsetti et al., 2004). *Gardia*-induced DGBI are associated with visceral hypersensitivity (Dizdar et al., 2007).

Finally, **cross-organ visceral sensitisation** between the stomach and another viscus, similar to what is described in IBS and PBS, will be detailed in a specific subchapter (1.5. Cross-organ sensitisation).

Most of the mechanisms discussed involve the ENS, the CNS, or the communication between both. The sensitivity of the digestive tract and its pathological aspect, visceral hypersensitivity, will be discussed in the following subchapter.

1.4. Pain and visceral nociception

Pain

Pain is defined by the International Association for the Study of Pain (IASP) as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage" (Raja et al., 2020). Pain and nociception are different phenomena; indeed, nociception can be inferred solely from the activity in sensory neurons following a stimulus (objective measure), while pain is a subjective experience, including psychological and social responses and not just biological factors. Chronic primary pain is defined as pain persisting for more than three months and is associated with significant emotional distress and functional disability (Treede et al., 2019). Chronic primary visceral pain states, such as IBS, are diseases in their own right and should be distinguished from chronic secondary visceral pain, a chronic pain secondary to an underlying condition originating from internal organs such as those in the abdomen (Aziz et al., 2019b).

Pain can be divided into three categories according to its mechanism: nociceptive pain, which is caused by damage to tissues; neuropathic pain, which is caused by damage to nerves; and nociplastic pain, in which altered pain processing and modulation play prominent roles (Kosek et al., 2016). In nociplastic pain, pain is usually more widespread and intense than expected, given observed damage to tissues or nerves, and is associated with other symptoms, such as fatigue, altered sleep, anxiety and depression. This pain occurs in conditions such as fibromyalgia, non-specific low back pain, tension-type headache, IBS, BPS, and so on. This pain category will respond poorly to peripherally-directed treatments such as anti-inflammatory drugs and opioids (Fitzcharles et al., 2021). Different types of pain may coexist.

Anatomy of gut nociception

Visceral nociception is a complex physiological process involving the intrinsic neurons of the ENS, the extrinsic afferent neurons and the CNS integration.

Anatomically, the GI tract is innervated by intrinsic neurons of the ENS and by the axons of extrinsic neurons, depending on the location of cell bodies within or outside the gut wall. The extrinsic innervation is composed of sensory afferent fibres and motor efferent (sympathetic and parasympathetic) fibres. The GI tract receives a parasympathetic supply from the vagus nerve and a sympathetic supply from splanchnic nerves; with the ENS, they form the three branches of the autonomous innervation of the gut. Sympathetic innervation arises from **prevertebral ganglia**, which comprise the coeliac, superior mesenteric and inferior mesenteric ganglia. Extrinsic sensory innervation of the digestive tract includes vagal and spinal pathways; the efferent pathways will not be detailed further. The cell bodies of the extrinsic primary afferent neurons (EPAN) are located in the sensory ganglia at the peripheral level: **dorsal root ganglia** (DRG) for spinal afferents (Haberberger et al., 2019), projecting to the dorsal horn of the spinal cord, and the **nodose ganglia** for vagal afferents, projecting to the brainstem, however, sympathetic, parasympathetic and spinal sensory pathways are integrated both anatomically and functionally. Indeed, the same nerves carry fibres for the ANS (visceral efferent fibres) as well as sensory fibres from the abdominal organs (visceral afferent fibres). All nerves carry sympathetic fibres except the pelvic splanchnic nerves, which carry parasympathetic fibres. A schematic representation of the innervation of the GI tract is shown in Figure 1.5.

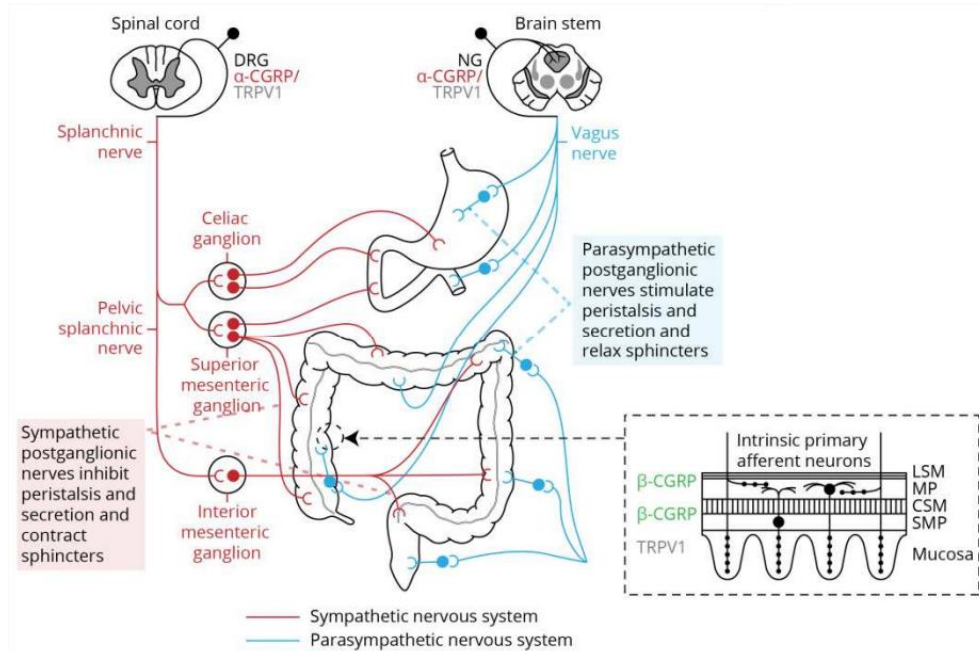


Figure 1.5. Representation of the autonomic innervation of the gastrointestinal tract.

Extrinsic spinal afferents only contain α -CGRP, whereas intrinsic enteric neurons express only β -CGRP (in the submucosal and myenteric plexuses). TRPV1 is present in DRG, NG and the parietal cells of the mucosa.

CGRP: calcitonin gene-related peptide, CSM: circular smooth muscle, DRG: dorsal root ganglion, LSM: longitudinal smooth muscle, MP: myenteric plexus, NG: nodose ganglia, SMP: submucosal plexus, TRPV1: transient receptor potential vanilloid 1.

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The enteric nervous system

The ENS represents the intrinsic innervation of the digestive tract, composed of hundreds of millions of neurons and glial cells bundled together, forming the most significant component of the ANS. The most recent study found 168 million neurons in the human ENS (Michel et al., 2022). It is often described as the “gut brain” or “second brain”. However, it contains a much lower number of neurons compared to the 86-120 billion neurons of the human brain

(Herculano-Houzel, 2009, von Bartheld et al., 2016), and it is closer to the 222 million neurons in the human spinal cord (Bahney and von Bartheld, 2018).

Anatomically, the ENS is composed of two networks of ganglia: the **myenteric plexus** (also called Auerbach's plexus) and the **submucosal plexus** (also called Meissner's plexus). The myenteric plexus is located between the longitudinal and circular muscle layers of the GI tract. In contrast, the submucosal plexus is located between the submucosa and the circular smooth muscle layer. However, there are regional and interspecies differences (Timmermans et al., 1997). Indeed, the submucosal plexus is absent in the oesophagus and the stomach, unlike the myenteric plexus, which extends from the oesophagus to the internal anal sphincter. This distinction in two main plexi is derived from studies in guinea pigs, the most commonly used animal in the study of the ENS. By contrast, three layers can be identified within the submucosal plexus in humans (from the mucosa to the serosa: Meissner's, intermediary, and Henle layers).

Physiologically, the ENS controls reflexes in the GI tract independently of the CNS. It has motor, sensory, absorptive, and secretory functions. Both plexi are engaged in smooth muscle motor control. In contrast, the myenteric plexus is only involved in peristalsis (both its initiation and control), and the submucosal plexus also controls the epithelium, forming a **neuro-epithelial unit** (Vergnolle and Cirillo, 2018).

The neuronal populations comprising the ENS have been characterised using different methods over the years: morphological, chemical, physiological, and, more recently, immunohistochemical and molecular. Historically, morphological classifications (Types I, II and III) were based on the work of Alexandre Stanislavovitch Dogiel, a Russian cytologist (Brehmer et al., 1999). Later, classifications were based on those neurons' chemical (neurotransmitters) and functional properties (Furness, 2000). We currently consider the ENS to contain three main groups of neurons constituting the plexi: **intrinsic afferent neurons**, **interneurons** and **effector neurons** (Brehmer, 2006). Intrinsic afferents neurons are sensory neurons that respond to stimuli to initiate reflexes. In contrast, efferent neurons are motor neurons that transmit information to effector cells such as those from arterioles, epithelium or smooth muscle. Interneurons integrate sensory information and modify those reflexes. Intrinsic afferent neurons can be further divided into two groups of neurons: the **intrinsic primary afferent neurons** (IPAN), located in both plexi, and the **intestino-fugal**

primary afferent neurons (IFAN), found only within the myenteric plexus (Szurszewski et al., 2002). There are also two types of effector neurons (with secretory and motor functions) in the submucosal plexus: cholinergic and non-cholinergic neurons. The former are immunoreactive to neuropeptide Y (NPY) and the latter to vasoactive intestinal peptide (VIP).

Descending neurons are VIP-positive and mainly innervate the mucosa, whereas ascending neurons are especially choline acetyltransferase (ChAT)-positive. Both circuits release acetylcholine and VIP, two strong secretagogues, potentiating secretion by acting on epithelial cells.

Nitrergic neurons (those using nitric oxide synthesised by nitric oxide synthase (NOS)) and cholinergic neurons (those using acetylcholine synthesised by choline acetyltransferase) are two separate neuron populations comprising the myenteric plexus. Most of the nitrergic neurons in the myenteric plexus are inhibitory motor neurons that innervate the smooth muscle. In contrast, cholinergic neurons are functionally diverse (including interneurons, intrinsic sensory neurons and excitatory motor neurons that innervate smooth muscle).

The **enteric glia** is mainly located within the ganglia of both plexi, but also near the nerve connections between them both and within villi of the mucosa, where they are in close contact with epithelial cells (Ruhl, 2005). Historically, the concept of *neuroglia* was introduced in 1858 by Rudolf Virchow as a substance giving its form to neurons. In 1899, A. S. Dogiel described glial cells within the intestinal wall. Still, those cells were only recognised as a distinct cell type in 1972 (Gabella, 1972) and named “enteric glial cells” a decade later by Giorgio Gabella (Gabella, 1981). In reality, enteric glial cells outnumber neurons in the ENS (approximately 4:1) (Gabella, 1981). Those cells play an essential role in maintaining the integrity of the mucosal barrier since their loss in transgenic mouse models results in neuronal degeneration, the disruption of the epithelial barrier, and inflammation (Bush et al., 1998). S100 protein is used as a pan-glial marker in the GI tract (Grundmann et al., 2019).

Note that different terms are used for the glia at the different levels of the nervous system. The cells composing the glia are called “enteric glial cells” in the ENS, “satellite glial cells” (SGCs) in the peripheral nervous system (DRG and nodose ganglia) (Hanani and Verkhatsky, 2021), and “glial cells” or “neuroglia” (comprising **microglia**, astrocytes, oligodendrocytes and ependymal cells) in the CNS (spinal cord, etc.).

The extrinsic primary afferent signalling

Primary extrinsic afferent neurons are sensory neurons responsible for reflexes and transmitting chemical, mechanical and thermal information. They are activated by stimuli present in the lumen of the GI tract and convey a signal to the CNS *via* three pathways, the **vagal, thoraco-lumbar and lumbo-sacral pathways**. The **vagus nerve** carries most sensory information between the GI tract and the brain. Indeed, most of the GI tract, from the oesophagus to the proximal colon, is innervated by the vagus nerve in humans, with vagal afferents projecting to the nucleus of the solitary tract (NTS or **nucleus tractus solitarii**) in the brainstem and then to different brain regions *via* the ascending pathways. Spinal afferents project to the gut *via* thoracic and lumbar **splanchnic nerves** at the trunk level, projecting to the T5-L2 segments of the spinal cord throughout the GI tract, and *via* **sacral** and **pelvic nerves** at the sacral level, as shown in Figure 1.6.

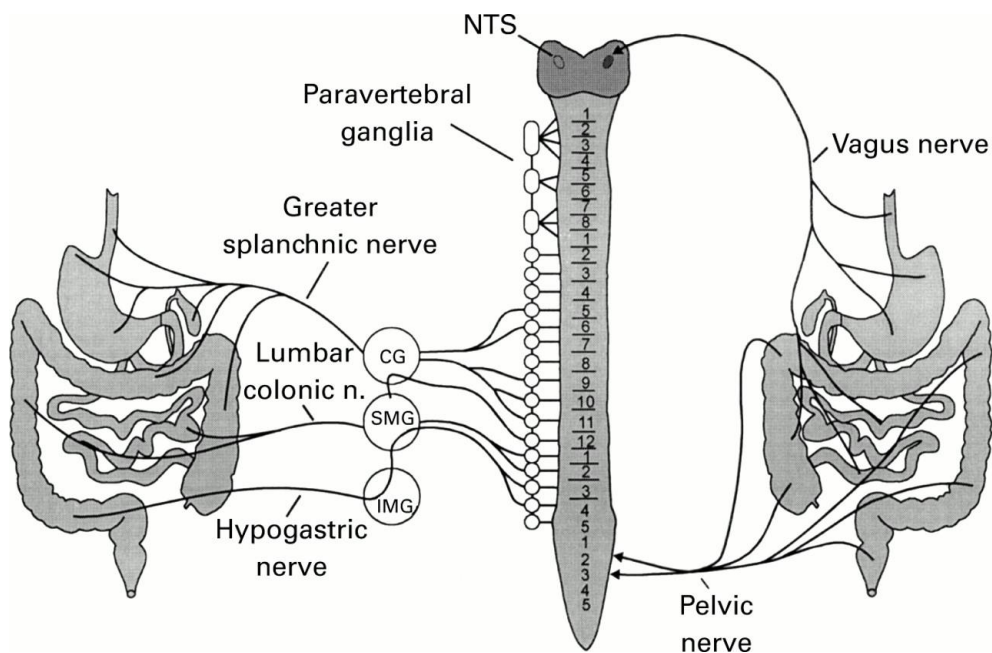


Figure 1.6. Representation of the innervation of the gastrointestinal tract.

CG: coeliac ganglion, IMG: inferior mesenteric ganglion, n.: nerve, NTS: nucleus tractus solitarii, SMG: superior mesenteric ganglion.

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The effect of the vagal innervation thus decreases progressively until it becomes sparse in the distal colon, where splanchnic nerves innervate the distal colon and pelvic nerves the rectum. Notably, the defecation reflex involves additional afferent pathways, explaining why the sensory innervation of the distal colon and the rectum is greater than that of the proximal colon (Kyloh et al., 2011). The vagal innervation of the rat GI tract is different from that of humans since the vagus nerve innervates the entire GI tract in rats, while it ends at the level of the proximal colon along the oral-to-anal gut axis in humans.

Primary afferents are mainly formed of nonmyelinated C fibres and, to a smaller extent, poorly myelinated A δ fibres. Since conduction speed depends on the amount of myelin surrounding their axons, C fibres convey the signal slowly (0.4-1.4 m/sec) compared to A δ fibres (5-30 m/sec). C fibres are polymodal, mechanical, heat-sensitive, and responsive to chemical stimuli (capsaicin, histamine, etc.). C fibres can be categorised as peptidergic and non-peptidergic fibres. **Peptidergic fibres** secrete substance P (SP, also called neurokinin-1 or NK1), encoded by the Tachykinin Precursor 1 (*TAC1*) gene, and calcitonin gene-related peptide (CGRP), express tropomyosin receptor kinase A (TrkA), a receptor which binds nerve growth factor (NGF) (NGF/TrkA signalling pathway), and mainly end in laminae I and II in the spinal cord. **Non-peptidergic fibres** express c-ret, a proto-oncogene, and tyrosine kinase, which binds glial cell-derived neurotrophic factor (GDNF) (GDNF/Ret signalling pathway) and mainly end in lamina II of the spinal cord. A δ fibres can also be further subdivided electrophysiologically as Type I (low threshold for mechanical and chemical stimuli, high threshold for temperature > 50 °C) and Type II (low threshold for temperature but high threshold for mechanical stimuli) fibres. At the colonic level in mice, six distinct classes of afferent nerves have been characterised from splanchnic and pelvic nerves based on their morphology, innervation of the layers of the colonic wall, functional and molecular profiles: serosal, muscular, mucosal, mesenteric, muscular/mucosal (Brierley et al., 2004) and mechanically insensitive “silent” (Prato et al., 2017). The contributions of the different afferent classes in the

development of post-inflammatory visceral hypersensitivity are diverse (Hughes et al., 2009).

The central nervous system

The CNS is made up of the spinal cord, the brainstem and the brain. These structures are made up of several cellular types (neuronal cells and glial cells). **Neurons** are differentiated based on their morphology and the neurotransmitters they secrete. **Glial cells** are a group composed of *astrocytes*, which have a support function; *oligodendrocytes*, which have a role in the myelination of the central axons; *ependymocytes*, which ensure the circulation of the cerebrospinal fluid (CSF); and *microglial cells*. These microglial cells have a different origin than other glial cells and are the main immune cells in the CNS. Indeed, all glial cells originate from the ectoderm (neural tube epithelium) in vertebrates. In contrast, microglial cells arise from primitive macrophages (erythro-myeloid progenitors that appear in the yolk sac outside the embryo) (Ginhoux et al., 2010).

Spinal cord

Grey matter mainly comprises neuronal bodies and is divided into ten laminae or layers. Laminae I to V are within the dorsal horn, and receive the sensitive afferents; Laminae VI and VII are at the centre of the cord; Laminae VIII and IX constitute the ventral horn, from which the motor efferent fibres leave; and finally, Lamina X surrounds the ependymal duct in which the CSF circulates. Sensory stimuli are analysed in the dorsal horn of the spinal cord, in Laminae I and II. The sensory neurons located in Laminae V, VII and X will also gauge the intensity of these stimuli. Sensory relays within the spinal cord form **spinal sensory-motor reflex circuits**, which may be in direct connection, or indirectly *via* interneurons, with motoneurons of the ventral horn of the spinal cord, to induce reflex contractions, but also with descending control (*corticospinal tract* in rodents).

Sensitive signals (nociceptive or not) are transported to brain structures by different ascending pathways. Two major ascending pathways are involved in the spinal cord: the **anterolateral pathway** (spinothalamic, spinoreticular and spinomesencephalic tracts), and the **dorsal column pathway**. A schema representing the ascending pathways involved in colorectal nociception is shown in Figure 1.7.

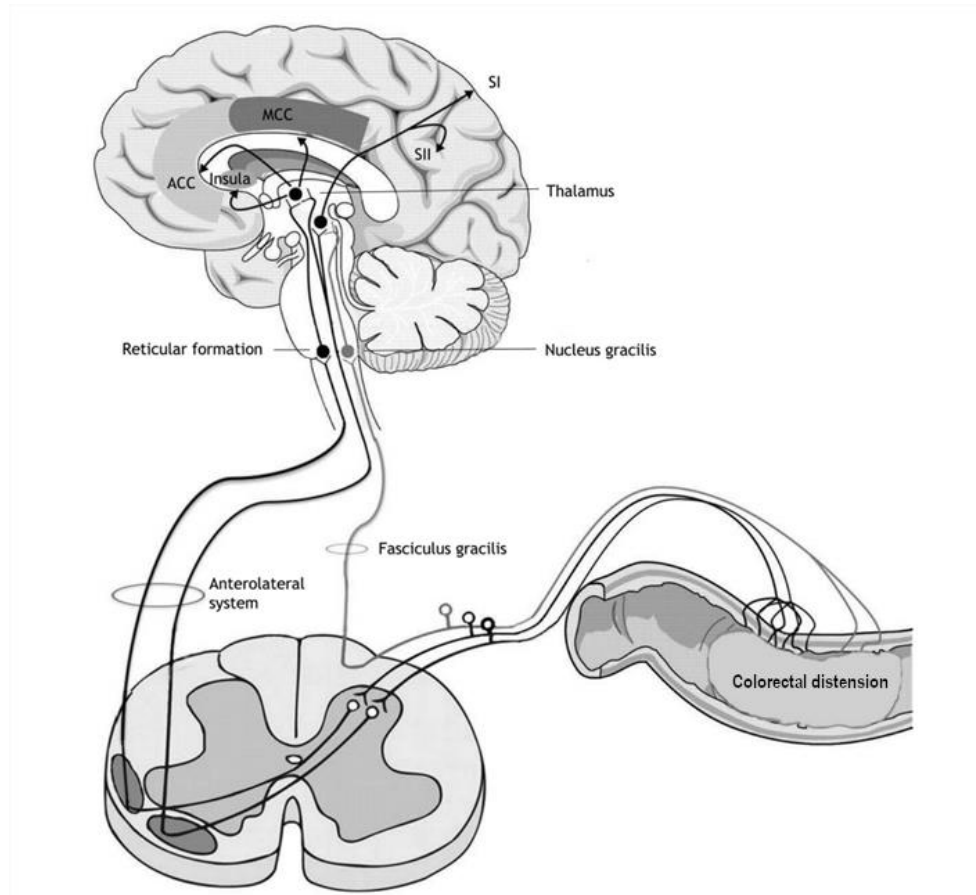


Figure 1.7. Overview of ascending pathways involved in visceral nociception following colorectal distension.

The anterolateral system includes the spinothalamic, spinoreticular, spinomesencephalic, spinotectal, and spinohypothalamic tracts. The fasciculus gracilis is a constituent of the dorsal column-medial lemniscal system.

ACC: anterior cingulate cortex, MCC: midcingulate cortex, SI: primary somatosensory cortex, SII: secondary somatosensory cortex.

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Ascending pathways (mainly the *spinothalamic tract* from the anterolateral pathway) conduct information on pain from the skin and visceral origins. These spinothalamic afferents project to the ventral posterior nuclei of the thalamus (VPL: ventral posterior lateral, and VPI: ventral posterior inferior), and the medial thalamus (*nucleus submedius*), which is consistently activated in brain imaging studies of rectal distensions in IBS (Tillisch et al., 2011). From these nuclei, pain signals spread to primary and secondary somatosensory cortices (SI and SII, respectively), and the prefrontal cortex, including the anterior cingulate cortex (ACC) and the midcingulate cortex (MCC). There are also projections to the periaqueductal grey matter, which connects with the medial thalamic nuclei and receives direct input from the ACC. Visceral pain location is diffuse, unlike somatic pain representation, which could explain why visceral sensation is poorly localised compared with somatic sensation.

The *spinoreticular tract* conducts sensory information from the spinal cord to the reticular formation in the brainstem. The reticular formation is mainly involved in the affective and motivational properties of noxious stimulation, such as for fibres arising from the medial thalamic nuclei for the spinothalamic tract.

The *spinomesencephalic tract* conducts sensory information from the spinal cord to various regions in the brainstem (including the periaqueductal grey matter, locus coeruleus, and reticular formation).

The dorsal column (or dorsal column–medial lemniscus pathway, DCML) system is an alternative spinal ascending nociceptive pathway, as suggested by the persistent sensation of visceral distension following extensive anterolateral chordotomy (White, 1943).

Brainstem

Sensory information from the lower half of the body is carried to the **nucleus gracilis**, and vagal sensory afferents project to the NTS, both in the brainstem.

The critical component of descending control of pain is the **periaqueductal grey matter**, the grey matter located around the cerebral aqueduct at the midbrain, since its stimulation leads to the repression of pain without affecting other sensory modalities. This circuit modulates pain transmission by acting on primary afferent nociceptive terminals and dorsal horn neurons responsive to nociceptive stimulation.

The **rostral ventromedial medulla** (RVM), also called the ventromedial nucleus of the spinal cord, is a group of neurons located near the **medulla oblongata** in the brainstem and involved in pain modulation. Pain signals are modulated by pain-inhibiting (“OFF-cells”) and pain-facilitating (“ON-cells”) neurons, two physiologically distinct classes of neurons (Neubert et al., 2004, Chen and Heinricher, 2022). This structure receives input from brain structures such as the amygdala, the hypothalamus, the cortex and the insula, both directly and indirectly via the periaqueductal grey matter. It sends descending inhibitory and excitatory fibres to the dorsal horn of the spinal cord.

Other areas involved in pain modulation in the brainstem are the **reticular formation**, composed of interconnected nuclei without being well-defined anatomically, and the **locus coeruleus**, the main site of synthesis of noradrenaline in the brain and involved in response to stress. The locus coeruleus is innervated by the cingulate cortex and the amygdala, allowing emotional pain to trigger a noradrenergic response.

Brain

Visceral nociceptive signals are integrated into the brain cortex. A large network of brain regions is involved in pain processing, and called the “**homeostatic afferent network**” (previously the “central pain matrix”), and is composed mainly of the insular cortex (posterior insula for the integration of somatic and visceral information and anterior insula for the integration of its affective component), the primary (SI) and secondary (SII) somatosensory cortices, involved in the sensory-discriminative processing of pain, the prefrontal cortex (ACC and MCC), and the thalamus, which are consistently activated in response to nociceptive stimuli of visceral origin (Sheehan et al., 2011, Tillisch et al., 2011). The **prefrontal cortex**, the **amygdala** and the hypothalamus are part of the **limbic system**, which is involved in emotion regulation. The **hypothalamus** links the CNS and the endocrine system *via* the pituitary gland.

Pain perception

The perception of pain intensity is modulated (increased or decreased) through emotional processes and descending control, involving cortical and brainstem areas.

Formerly, the “neuromatrix” theory of pain asserted that a fixed brain network was active in pain perception (Melzack, 2001). It is now supposed to come from a dynamic cerebral network, called “cerebral signature”, which varies according to individuals (Tracey and Mantyh, 2007).

Emotional modulation of pain perception

The “**emotional arousal network**” engaged in the emotional processes modulating visceral pain sensations (e.g. anticipatory anxiety or fear) is also activated following nociceptive stimuli of visceral origin. This network includes the locus coeruleus complex, amygdala, hypothalamus, parahippocampal gyrus, perigenual anterior cingulate cortex (pACC), anterior insula, and orbitofrontal cortex (Tillisch et al., 2011).

Descending control of pain perception

Pain perception is controlled centrally by the “**PAG-RVM**” system, involving the **periaqueductal grey matter** and the **rostral ventromedial medulla**. This system may turn off nociceptive signals under normal conditions *via* their connections with inhibitory interneurons in the spinal cord (Zhuo, 2008).

The **diffuse noxious inhibitory controls**, known as the “pain inhibiting pain” phenomenon, mean that a painful stimulus which is applied to a part of the body distant from the actual site of pain inhibits neurons within the dorsal horn of the spinal cord that are actively responding to chronic pain, as seen in visceral hypersensitivity (King et al., 2009). IBS patients are known to have a deficit of diffuse noxious inhibitory controls, which correlates with symptom severity (Bouhassira et al., 2013).

Gut perception & visceral nociceptive signalling

Communication between the gut and the CNS (the “**gut-brain axis**”) includes three different **pathways**: neuronal pathways (see previous chapter on Anatomy of gut nociception), neuroendocrine pathways (mainly the hypothalamo-pituitary-adrenal or stress axis), and neuroimmunological pathways. The gut microbiota is also required for visceral nociception, as demonstrated by experiments with germ-free mice (Luczynski et al., 2017). There is increased evidence for a microbiota-gut-brain axis, with microbiota modulating central

responses. For instance, ClpB, a protein mimetic of alpha-melanocyte-stimulating hormone (α -MSH) produced after nutrient-induced *E. coli* growth, may signal meal termination (Breton et al., 2016).

The gut function involves multiple **reflexes** in response to luminal stimuli. This complex regulation is mediated both by neuronal and hormonal signalling. Most ascending visceral information is unconscious, except sensations of hunger, satiety, and the urge to defecate. Under pathological circumstances, like DGBI, gut stimuli may induce conscious perception and painful sensations. Responses to intestinal stimuli depend on the intensity of the stimulation and the number of activated receptors (summation phenomenon). Still, neurons involved in the control of GI tract functions and visceral perception, and their nerve terminals, are also modulated by different signals: mechanical changes (distension or contraction), different mediators in the lumen, macronutrients (especially lipids), stress, the immune system, gut microbiota, the enteric glia, the circadian period, the feeding state, etc. Visceral perception is also modulated by cognitive and psychological mechanisms (Whitehead and Palsson, 1998), like anticipation (Accarino et al., 1997), anxiety (Ford et al., 1995) and increased vigilance to painful stimuli (Jarrett et al., 2014). Describing the neuronal control of digestive tract functions, especially of the stomach, is beyond the scope of this introduction and will not be detailed further (Azpiroz et al., 2014).

Numerous mediators and receptors are involved in visceral pain processing. **Nociceptors** in the gut transmit pain signals to the CNS. Those nociceptors belong to three families:

- neurotransmitter receptors (acetylcholine nicotinic, cannabinoid, opioid, γ -aminobutyric acid (GABA_A, GABA_B, and GABA_C), glutamate (both ionotropic & metabotropic), glucocorticoid, etc. receptors);
- inflammatory receptors (bradykinin, cholecystokinin, cytokine, leukotriene, prostanoid, and tachykinin receptors [e.g. neurokinin-1 receptor or NK1R], nitric oxide signalling, cyclooxygenase, lipoxygenase, etc.);
- ion channel receptors (transient receptor potential vanilloid (TRPV) and purinergic (P2X) receptors, voltage-gated calcium channels (CaV), voltage-gated potassium (KV) channels, voltage-gated sodium (NaV) channels, etc.).

In the stomach, gastric wall tension is the determinant for sensing gastric **distension** (Distrutti et al., 1999, Piessevaux et al., 2001). Perception of changes in the wall tension of the proximal stomach is independent of the propagation of fundic contractions to the antrum (Piessevaux et al., 2001). Meal ingestion induces gradual distension of the gastric wall, which leads to the first signal to control meal size (Wang et al., 2008b). Postprandial satiation is linked to the filling of the antrum (Jones et al., 1997).

In the colorectum, visceral pain is usually caused by mechanical distension rather than heating, cutting, or pinching (which suggests pain originates from the skin). Mechanotransduction, the process of converting mechanical stimuli to the intestinal wall into neuronal signals, is mediated in mechanosensitive cells by mechanoreceptors and mechanotransducers (Yang et al., 2022b). Sensitive signals (nociceptive or not) from the colon are then transported to the brain by different ascending pathways, as shown in Figure 1.7.

Visceral hypersensitivity

Visceral hypersensitivity corresponds to increased nociception in the viscera by definition. Physiologic stimuli can therefore induce discomfort due to increased intestinal perception. Visceral hypersensitivity was first described in the colorectum in a subset of IBS patients almost half a century ago by James Ritchie (Ritchie, 1973), as shown in Figure 1.8.

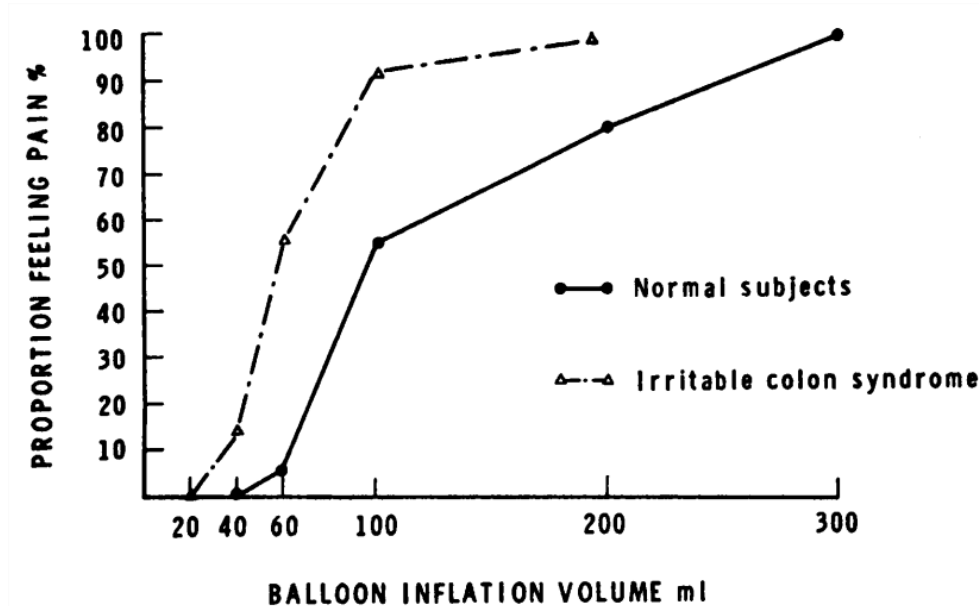


Figure 1.8. Onset of pain at different volumes of balloon inflation in healthy subjects vs patients suffering from irritable bowel syndrome.

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Although first described in IBS, hypersensitivity to gastric distention has also been described in FD (Mearin et al., 1991, Coffin et al., 1994), as shown in Figure 1.9. Gastric hypersensitivity was found in 34% of FD patients in tertiary care (Tack et al., 2001). In the stomach, however, the effects of distension depend on wall tension (Distrutti et al., 1999, Piessevaux et al., 2001). Therefore, the measurement of hypersensitivity to gastric distension should be interpreted with caution. The pathomechanisms involved in the development of gastric hypersensitivity need to be better understood. Both central and peripheral mechanisms have been suggested as implicated, with peripheral sensory alterations dominating in some patients and disturbed central processing dominating in others. The level of visceral hypersensitivity is proportional to the GI symptom severity in FD and IBS patients, independently of anxiety, depression, and somatisation (Simren et al., 2018).

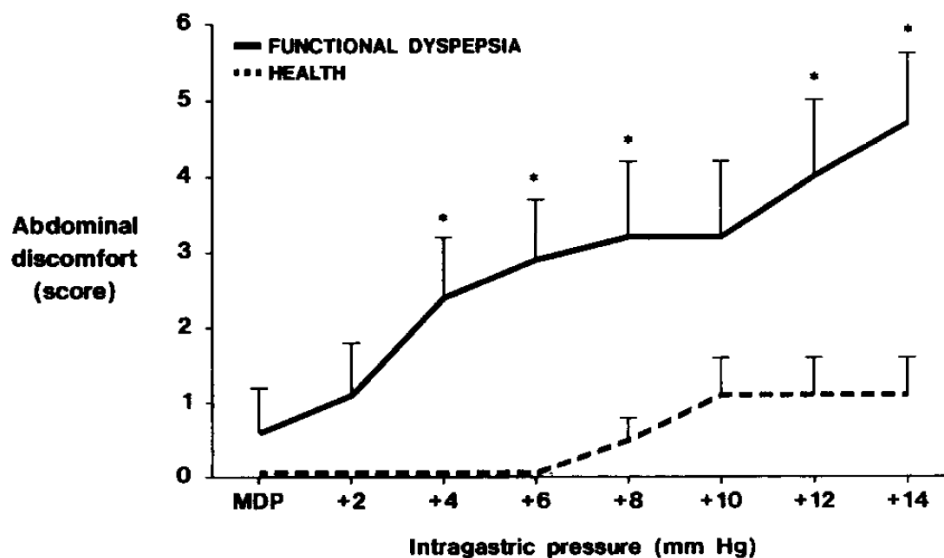


Figure 1.9. Onset of abdominal discomfort at different intra-gastric pressures in healthy subjects vs patients suffering from functional dyspepsia.

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There is contradictory data concerning the specificity of visceral hypersensitivity to the organ involved in the pathophysiology of different pain syndromes. Historically, hypersensitivity has first been shown to be limited to the stomach in FD (Coffin et al., 1994). Then, there has been some evidence that visceral hypersensitivity could be diffuse and not segmental in IBS and FD patients (Trimble et al., 1995). However, distension thresholds in the small intestine (first perception and maximum tolerated pressure) do not differ between patients with FD alone, IBS alone or FD+IBS overlap (Holtmann et al., 1997). More recently, visceral hypersensitivity to distension has been shown to be organ-specific in patients exhibiting IBS or FD alone, but pan-intestinal in patients with overlapping FD-IBS (Bouin et al., 2004).

The mechanisms underlying visceral hypersensitivity are poorly understood. Sensitisation means increased sensitivity to stimuli; this phenomenon may occur in the peripheral or central nervous systems. All nociceptors can be sensitised, leading to hyperalgesia (increased pain following a stimulus that usually causes pain) with or without allodynia (pain following a stimulus that does

not normally cause pain). Peripheral sensitisation is due to reduced thresholds and the amplified responsiveness of nociceptor terminals at the level of the primary sensory neurons, after they have been exposed to inflammatory mediators and damaged tissue; peripheral sensitisation is therefore limited to the site of tissue injury, and generally requires ongoing insult for its maintenance. Conversely, central sensitisation is mediated by integrating new inputs into nociceptive pathways and by increased spinal neurons' sensitivity, which produces hypersensitivity to pain in non-inflamed tissues long after the initial cause has disappeared (Latremoliere and Woolf, 2009). The concept of central sensitisation has been introduced in the last paragraph of the section about the Pathophysiology of FD and is further discussed in the following subchapter (see Supra-spinal sensory crosstalk).

The sensitisation of a single nociceptive pathway is unlikely to explain pain in DGBI, especially in IBS, for several clinical reasons: (1) IBS patients often complain of symptoms (bloating, abdominal discomfort, etc.) other than abdominal pain, (2) pain in those disorders is chronic, and cannot, therefore, be secondary to prolonged distension of the lumen at painful levels, (3) a single nociceptor activation may not be sufficient to make pain chronic, suggesting the interplay of modulatory factors such as central integration. The nociceptors involved in visceral pain perception (see the previous chapter about Gut perception & visceral nociceptive signalling), and their corresponding mediators, are also involved in the development of visceral hypersensitivity.

Gender could also play a role since women are known to be more susceptible to stress-related disorders (Adeyemo et al., 2010). For example, the female-to-male ratio is about 2:1 in IBS (Adeyemo et al., 2010). Gastrointestinal symptoms, including visceral pain, are more commonly experienced during the late luteal and menses phases of the cycle (Whitehead et al., 1990). Female hormones could also affect visceral sensitivity. Indeed, ovarian hormones, especially oestradiol, are key modulators of visceral sensitivity, and mediate the development of visceral hypersensitivity following unpredictable early life stress in female rats (Chaloner and Greenwood-Van Meerveld, 2013).

One of the pathomechanisms explaining the development of visceral hypersensitivity is its transmission from a distant organ under stress, a phenomenon known as cross-organ sensitisation.

1.5. Cross-organ sensitisation

Cross-organ sensitisation includes viscerosomatic and viscerovisceral cross-sensitisations. Mechanisms underlying cross-organ sensitisation are mainly neurological, through convergence-projection mechanisms, by analogy with what is described in referred viscerosomatic pain. Referred pain means pain perceived at another location from the location of the painful stimulus. In the “convergence-projection theory”, visceral and somatic afferent neurons converge in the dorsal horn of the spinal cord. Clinically, this theory can explain visceral pain referred to the skin, in particular. The visceral fibres have several roots, which explains the presence of pain referred to by several metamers. On the other hand, the theory of reflex arcs explains the presence of motor responses on the same metamer following a painful stimulus. The pain signalling passes through an afferent pathway and triggers a motor response on the same metamer *via* a somatic efferent pathway (particularly to muscles). Finally, it has been shown that visceral pain can be transmitted to the vegetative system through visceral-visceral convergences, similar to the reflex arc described above. Clinically, this helps explain the vegetative skin phenomena that occur in a region during pain (sweating disorders, redness). The rest of this subchapter will focus on visceral cross-sensitisation.

Cross-organ visceral sensitisation

Cross-organ visceral sensitisation is defined as the transmission of hypersensitivity to stimuli from a primarily injured visceral organ to a distant viscus that is not otherwise affected by the disease process affecting the first. This inter-organ sensory crosstalk usually involves an inflammatory insult to a primary organ, sparing the distant one, and shared sensory nerve pathways at the prespinal, spinal, and supraspinal levels. This phenomenon has been studied for over a decade. It could explain the occurrence of some overlapping functional disorders from the same body level, especially the pelvis. In particular, it has been involved in the overlap between IBS and BPS, focusing on bladder-colon cross-sensitisation in animal models (Ustinova et al., 2006).

Mechanisms of visceral cross-sensitisation are complex and probably involve peripheral and central mechanisms (Brumovsky and Gebhart, 2010). Furthermore, central sensitisation can be spinal or supra-spinal. Interactions at the origin of cross-sensitisation can therefore occur *via* three different **neural pathways**:

- convergence of afferent signals within a dorsal root ganglion or nodose ganglion;
- convergence of afferent signals in the spinal cord;
- convergence of afferent signals in the brain.

Peripheral (pre-spinal) cross-sensitisation

Peripheral sensitisation of sensory nerve terminals could occur in different organs independently, but this is not cross-sensitisation. Peripheral cross-sensitisation involves, on the contrary, either EPAN from two peripheral organs whose somata are located in the same DRG (**convergent afferents**) or EPAN with axonal branches innervating two different organs (**dichotomising afferents**). The sensitisation of adjacent EPAN that innervate distant organs within a single DRG is thought to be the main mechanism of peripheral cross-sensitisation and involves SGCs and macrophages (Qiao and Tiwari, 2020), as described in the next subchapter (1.6. Role of microglia in visceral sensitivity processes), since somata of different neurons do not form synapses within DRG. The example of bladder-colon cross-sensitisation at the peripheral level through convergent DRG neurons is shown in Figure 1.10.

Somata of EPAN in DRG will generate action potentials which are transmitted in two directions: an orthodromic signal to the spinal cord will modulate the sensory activity, and an antidromic signal will explain the release of mediators at the site of nerve terminals. This antidromic activity of dichotomising afferents explains the phenomenon of **neurogenic inflammation** since pre-spinal convergence of sensory information from distinct organs to a single neuron could lead to the release of inflammatory mediators in the unaffected organ (Sorkin et al., 2018).

Spinal cross-sensitisation

Spinal segmental cross-sensitisation

Axons from the somata of sensory EPAN exit DRG to reach the dorsal horn of the spinal cord. Signals are transmitted to secondary afferent neurons (SAN), which relay information to the brainstem and the brain. There is sensory **spinal convergency** in the spinal cord of inputs from different peripheral organs. The sensitisation of spinal neurons involves interneurons and microglial cells, and explains the dorsal root reflex (cf. convergence-projection theory).

Wallerian degeneration, the degeneration process resulting from the section of a nerve fibre, could also be involved in cross-sensitisation to a lesser extent. Indeed, L5 spinal nerve transection induced uninjured L4 DRG hypersensitivity in rats (Chen et al., 2019).

Spinal trans-segmental cross-sensitisation

The mechanisms described above would only explain cross-activation of EPAN for which somata are localised in the same DRG or organs for which there is spinal convergence of sensory fibres but could not explain why a subgroup of IBS patients develop leg pain and skin hypersensitivity of the feet, for example (Stabell et al., 2013). Indeed, EPAN from the colon and lower extremities relay to different spinal cord segments. If viscerosomatic cross-organ sensitisation could explain this phenomenon, it should involve a central process with sensory inputs relaying in the spinal cord with lower extremity sensory reflex circuits. This spinal trans-segmental crosstalk occurring in the dorsal horn of the spinal cord would require chemical mediators to sensitise the central nerve endings of EPAN of a distant organ for cross-sensitisation to occur.

The transmission of sensory information occurs *via* astrocytes, which form a network within the spinal cord through **gap junctions**, and microglial cells.

Besides synaptic transmission, active compounds are also spread by **volume transmission**. Indeed, neurotransmitters are also released from varicosities and can diffuse into extracellular space, a phenomenon called **extrasynaptic exocytosis**. Extracellular vesicles (exosomes) released by DRG neurons and nerve terminals also carry compounds to surrounding cells.

Another mechanism involved in the trans-segmental crosstalk is the **sprouting of nerve fibres**. Indeed, the sprouting of CGRP-immunoreactive

peptidergic nerve fibres occurs in the spinal cord following 2,4,6-trinitrobenzene sulphonic acid (TNBS)-induced colitis (Qiao and Grider, 2009).

Spinal central sensitisation is characterised by the activation of the N-methyl-D-aspartate (NMDA) receptor (Zhou et al., 2011). Upregulation of its NR1 subunit, in particular, is found in rats with colonic hypersensitivity induced by TNBS colitis (Zhou et al., 2009). Other pathways, like the phosphatidylinositol 3-kinases/protein kinase B/mammalian target of rapamycin (PI3K/AKT/mTOR) pathway, an important intracellular signalling pathway which regulates the cell cycle, are also implicated (Kay et al., 2013). Both activations of the NMDA receptor and the PI3K/Akt/mTOR pathway are triggered by CGRP and promote the phosphorylation of the cAMP response element-binding protein (CREB), an important transcription factor (Kay et al., 2013).

In summary, a visceral inflammatory insult could activate the Akt pathway and the NMDA receptor through the release of CGRP and induce spinal central sensitisation and spinal trans-segmental sensory crosstalk, primarily *via* the sprouting of central axons from EPAN.

Supra-spinal sensory crosstalk

The main mechanisms driving pain amplification in the brain are dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis and central (supra-spinal) sensitisation.

Acute stress increases the activity of the **HPA axis**, resulting in higher serum cortisol levels. On the contrary, repeated stress, especially chronic pain, is associated with suppression of the activity of the HPA axis. Patients suffering from chronic pain conditions are more likely to have a history of abuse (Nicol et al., 2016). Traumatic events in early life could alter the function of the HPA axis and influence its effects on nociceptors (Burke et al., 2017). Increased mast cell infiltration and degranulation could consequently sensitise nearby nerve terminals.

Central sensitisation refers to the increased excitability of neurons involved in central nociceptive pathways in response to painful or non-painful stimuli, manifesting clinically as hyperalgesia and allodynia, respectively. It is increasingly seen as a key mechanism in the pathophysiology of chronic pain disorders. Central sensitisation can be assessed by conditioned pain modulation (highlighting a decrease in the perception of pain following the application of a

stimulus in a different area, which testifies to descending inhibition of nociceptive signals, which was described further in the paragraph about Descending control of pain perception previously), quantitative sensory testings (application of von Frey filaments and radiant heat to assess mechanical and thermal pain thresholds respectively, for example), brain imaging (see the subchapter about Functional brain imaging in Chapter 9), and by questionnaires (central sensitisation inventory, highly sensitive person scale, etc.) in humans.

Central sensitisation can involve different mechanisms: impaired processing of sensory information in the brain, deficient mechanisms of descending control of pain, increased activity of pain pathways, temporal summation of pain inputs, potentiation of synaptic transmissions in the ACC on the long-term, etc. Central sensitisation related to chronic pain manifested as changes in the brain connectivity of the pain matrix in a rat model of chronic pain, mainly involving the anterior cingulate and the somatosensory cortices (Spisak et al., 2017). Patients with chronic pain conditions have increased grey matter volume in brain areas involved in pain processing (Kutch et al., 2017). This increase is associated with more widespread pain and comorbidities (Kutch et al., 2017). Higher grey matter density within the somatosensory cortex, amygdala, and hippocampus has been described in BPS patients (Kairys et al., 2015). Changes in the ACC and insula cortex can decrease descending inhibitory control and facilitate the transmission of nociceptive signals. For example, long-term potentiation and cortical plasticity in these areas have been described following peripheral nerve injury (Zhuo, 2008). Furthermore, the activation of microglial mitogen-activated protein kinase (MAPK)-p38 protein at the RVM was responsible for utero-colonic cross-sensitisation in an acute model (Chen et al., 2015). Finally, the involvement of the emotional arousal network could lead to central pain amplification. It could explain, in particular, why IBS patients have increased stress, anxiety, vigilance, and altered autonomic responses (Tillisch et al., 2011).

Example: cross-sensitisation between pelvic organs

Pelvic organ cross-sensitisation can occur between the urinary, genital and GI tracts. In the clinic, it can explain the coexistence of PBS, IBS, vulvodynia or scrotal pain in some patients.

Using animal models is essential to understand the mechanisms underlying cross-organ visceral sensitisation. It has been shown that visceral hypersensitivity can be transmitted between different pelvic organs in animals. In particular, bladder-colon cross-sensitisation is well described and could explain the clinically observed overlap between BPS and IBS. The presence of a subpopulation of colon-bladder convergent DRG neurons and their persistent hyperexcitability after colonic inflammation provides a basis for pelvic organ cross-sensitisation (Malykhina et al., 2006), as shown in Figure 1.10. Zymosan-induced neonatal cystitis also induces colonic hypersensitivity in adult rats (Miranda et al., 2011). Animal models of cross-organ visceral sensitisation are described in Chapter 9 (9.2. Animal models of cross-organ visceral sensitisation).

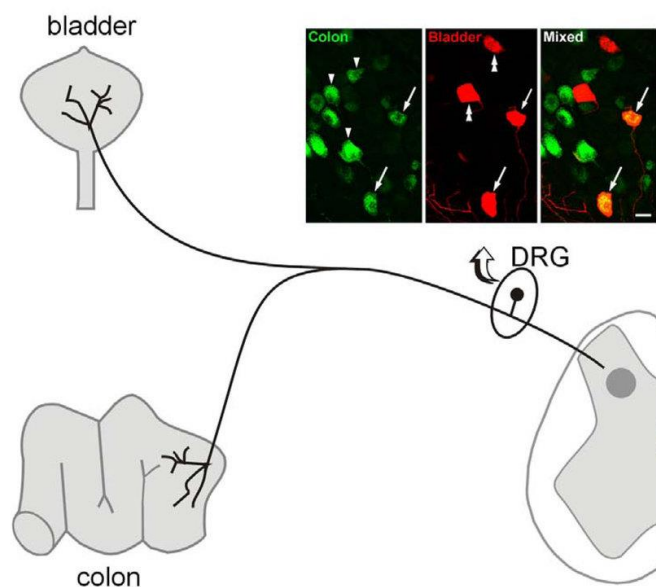


Figure 1.10. Putative mechanisms of cross-sensitisation between the bladder and the colon, depicting the subpopulation of colon-bladder convergent DRG neurons. DRG: dorsal root ganglion.

Adapted from Brumovsky & Gebhart (Brumovsky and Gebhart, 2010) with permission from Elsevier. Copyright © 2009 Elsevier B.V. All rights reserved.

Increasing evidence indicates the key role of interactions between neurons, glial cells and immune cells in sensory cross-activation at different levels (Qiao and Tiwari, 2020), which will be discussed in the following subchapter.

1.6. Role of microglia in visceral sensitivity processes

Microglial cells are the resident macrophage cells of the CNS and act as the main immune defence at that level (Uriarte Huarte et al., 2021). Microglial cells are part of the glial cells of the CNS, along with astrocytes, oligodendrocytes and ependymal cells.

Microglial cells are classically categorised in resting versus activated states (or M1 versus M2 states). Microglial **morphology** was used to differentiate between homeostatic and activated microglial cells. However, the assessment of microglia morphology is subjective. Quantifying microglial cells was therefore used as a surrogate for microglial activation. More recently, multiple states and functions of these cells have been described. It is now accepted that **multiple states** based on morphological, transcriptomic, proteomic, metabolomic and epigenetic assessments can coexist: disease-associated microglia (DAM), lipid-droplet-accumulating microglia (LDAM) in ageing, white matter-associated microglia (WAM), axon tract-associated microglia (ATM), etc. (Paolicelli et al., 2022). Microglial cells are implicated in neurogenesis, synapse remodelling, neuronal function, tissue repair, blood-brain barrier permeability, vasculogenesis, inflammation, and myelination (Paolicelli et al., 2022).

Different **biomarkers** of microglial cells have been described. The fractalkine receptor CX3CR1 is considered a microglial-specific receptor, especially since monocytes rarely enter the spinal dorsal horn (Gu et al., 2016). In mice, cells which express CX3CR1 on their surface in mice are monocytes, some natural killer (NK) cells, circulating and skin resident dendritic cells, microglial cells (Jung et al., 2000) and differentiated cytotoxic CD8+ T cells (Gerlach et al., 2016). However, this receptor is not expressed in resting tissue macrophages (like hepatic Kupffer cells, splenic and peritoneal macrophages), astrocytes, oligodendrocytes, neutrophils, eosinophils, B lymphocytes, and other T cells. A transgenic mouse strain (CX3CR1^{gfp+}), in which the CX3CR1 gene is replaced with the gene encoding the green fluorescent protein (GFP) in a heterozygote state, can be used to assess cells that express this receptor. Other methods have been used to identify microglial cells. In particular, immunofluorescence staining for ionised calcium-binding adaptor molecule-1 (Iba1), a microglia/macrophage marker, and transmembrane protein 119 (TMEM119), a resident microglia marker, has been

alleged to help distinguish resident microglia from blood-derived macrophages in the CNS of mice, the first being Iba1(+)/TMEM119(+) and the latter Iba1(+)/TMEM119(-) (Gonzalez Ibanez et al., 2019). However, TMEM119 is not exclusively expressed by microglia nor labels all microglia, especially under cellular stress conditions (Vankriekelsvenne et al., 2022). A purinergic receptor (a subtype of adenosine diphosphate (ADP) receptor), P2Y₁₂, playing an essential role in platelet activation and blood clotting and specifically inhibited by the active metabolite of clopidogrel (Plavix®), was found to be exclusively expressed by microglial cells in the CNS of mice (Butovsky et al., 2014).

The colony-stimulating factor-1 receptor (**CSF-1R**) regulates the proliferation, differentiation, and survival of microglia, and is also a microglial biomarker. Inhibitors of CSF-1R (e.g. PLX-3397 and PLX-5622) efficiently eliminate microglia at the CNS level in mice (Liu et al., 2019), while others (e.g. GW2580) prevent its activation without altering their number (Soto-Diaz et al., 2021). The receptor CSF-1R is not specific to microglia but is also expressed in monocytes and macrophages. Inhibitors of CSF-1R affect peripheral macrophages and not only the microglia (Lei et al., 2020). Those which eliminate microglial cells are mainly used to obtain pure cell cultures.

The **role** of spinal microglia is increasingly described in visceral hypersensitivity. Indeed, the activation of microglia is a critical step in the onset and maintenance of hypersensitivity and allodynia in animal models of inflammatory and neuropathic pain (Mika et al., 2013). Chronic psychological stress (e.g. water avoidance stress or WAS, see chapter 9.1. Animal models of visceral hypersensitivity) also leads to microglial activation in the lumbar spinal cord in animal models (Bradesi et al., 2009). This activated microglia can be blocked by a MAPK-p38 inhibitor, like SB203580, or by minocycline, a microglia inhibitor (Bradesi et al., 2009). Conversely, fractalkine (CX3CL1 or FKN), a chemokine used as a microglial activator, can induce visceral hypersensitivity in rats (Bradesi et al., 2009). The fractalkine receptor (CX3CR1) is known to be expressed by microglial cells (Verge et al., 2004). The development of colonic hypersensitivity in rats following WAS is enhanced through the FKN/CX3CR1 axis and can be blocked by minocycline (Bradesi et al., 2009).

Minocycline is an antibiotic of the tetracycline family. Its biological half-life is about 16-18 hours. It has a high CNS penetrance, an advantage in CNS infections such as Lyme disease, explaining its main side effects (dizziness, nausea,

vomiting, etc.). Besides its bacteriostatic activity, it has anti-inflammatory, anti-apoptotic and neuroprotective properties (Zemke and Majid, 2004). It has been used for treating acne vulgaris for a long time. Minocycline inhibits microglia as part of its anti-inflammatory properties. Still, this effect is not selective since it affects peripheral immune cells (monocytes, macrophages, T-cells and neutrophils) (Moller et al., 2016).

Microglial remodelling in the central nucleus of the amygdala contributes to chronic stress-induced visceral hypersensitivity *via* microglial p38 mitogen-activated protein kinase (MAPK) activation, glucocorticoid receptor dysfunction, and synaptic plasticity (Yuan et al., 2020b). Inhibition of microglial activity in the central nucleus of the amygdala is sufficient to attenuate stress-induced visceral hypersensitivity (Yuan et al., 2020b).

Interactions between neurons, microglial cells and immune cells have a crucial role in cross-organ sensitisation (Qiao and Tiwari, 2020). In the previous subchapter (1.5. Cross-organ sensitisation), we have seen that cross-sensitisation of adjacent sensory EPAN that innervate distant organs within a single DRG is the main mechanism underlying cross-organ sensitisation. However, EPAN are anatomically distinct within DRG, with no synaptic connections. They are surrounded by SGCs and macrophages, forming a **“neuron-glia-macrophage” triad**. Therefore, the preferred hypothesis proposes that diffusible chemical mediators originating from the primarily sensitised neurons are secreted within the sensory ganglia (DRG or nodose ganglia) and received by the neighbouring cells. Therefore, sensory cross-activation within this triad would be due to paracrine and autocrine interactions (Amir and Devor, 1996). Numerous paracrine/autocrine mediators are indeed released from the somata of neurons within DRG under inflammatory or pain conditions: adenosine triphosphate (ATP), substance P, CGRP, glutamate, GABA, galanin, nitric oxide (NO), brain-derived neurotrophic factor (BDNF), etc. (Matsuka et al., 2020).

A mechanistic model of cross-organ sensitisation with intra-ganglionic crosstalk and spinal central sensitisation is shown in Figure 1.11.

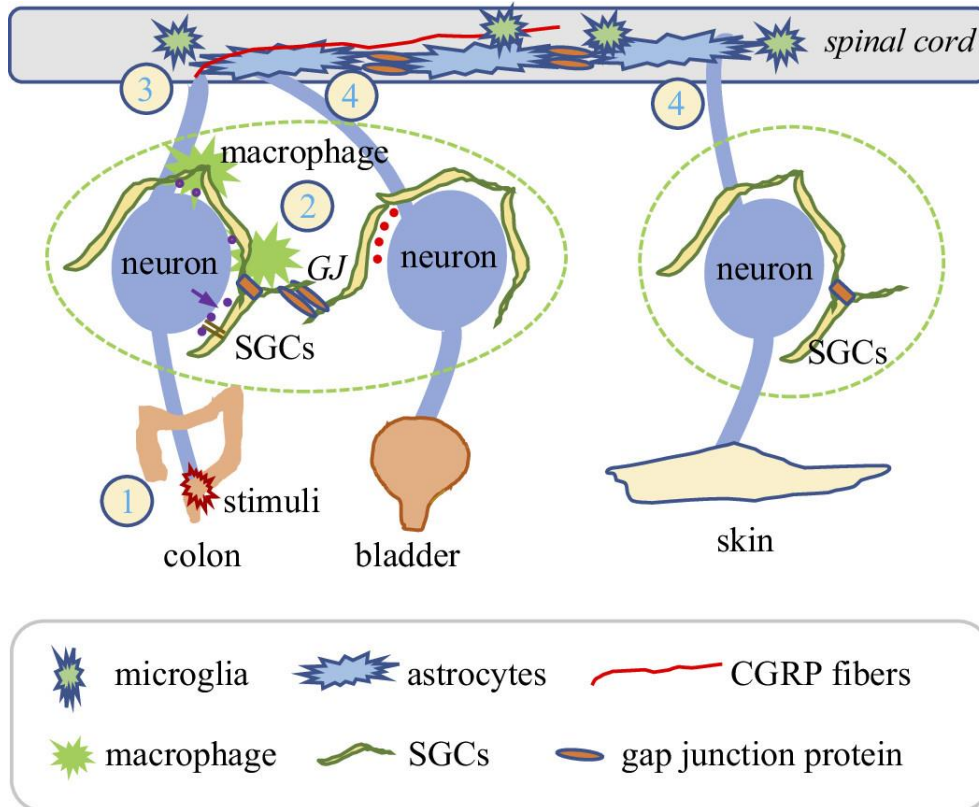


Figure 1.11. Mechanistic model of cross-organ sensitisation with intra-ganglionic crosstalk and spinal central sensitisation.

Following an insult of a specific organ (e.g., chemical colitis of the distal colon) (1), mediators released by the primary afferent neurons of that organ act on adjacent macrophages and SGCs within the DRG, which transmits sensory information to neighbouring neurons, resulting in cross-activation of these sensory neurons belonging to a distant organ (2). Mediators released in the dorsal horn of the spinal cord induce morphological changes, proliferation and differentiation/hypertrophy of the microglia and astrocytes (3). Activation of non-neuronal cells (macrophages, SGCs, microglia and astrocytes) causes neuroinflammation. The formation of gap junctions between astrocytes also allows the transmission of information to remote areas of the spinal cord. Secretion of mediators at this level leads to retrograde sensitisation of central terminals of primary afferent neurons of an organ innervated in another segment of the spinal cord (e.g., colon and lower extremities) (4).

CGRP: calcitonin gene-related peptide, DRG: dorsal root ganglia, GJ: gap junction proteins, SGCs: satellite glial cells.

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Clinically, one of the most common comorbidities associated with FD is IBS. The possibility of cross-sensitisation between different organs naturally leads to the question of whether a phenomenon of cross-sensitisation between the colon and the stomach could explain the overlap of those disorders. State of the art on that question will be the subject of the following subchapter.

1.7. Cross-organ sensitisation between the upper and lower gastrointestinal tracts: state of the art

The organs involved in cross-sensitisation processes are generally either from the “thorax-upper digestive tract” group (oesophagus, heart, lower respiratory tract, stomach, duodenum and gallbladder) or from the “pelvis-lower digestive tract” group (colon, rectum, ureters, bladder, pelvic urethra, uterus and prostate). On the other hand, the existence of cross-sensitisation between the organs in each of these two groups, although described, is poorly studied.

Physiological links between the upper and lower GI tracts, mediated by humoral and neural pathways, have been described in animals and humans.

The most studied link is the one between colonic processes and gastric physiology. In animals, rectal distension inhibits gastric tone in a volume-dependent manner and affects gastric accommodation in dogs (Lei et al., 2005). This effect does not appear to be mediated by the sympathetic nervous system. In rats, distension of the proximal colon inhibits GE (Martinez et al., 2006). Colonic distension also inhibits the gastric relaxation, suggesting a colo-gastric relationship in rats (Uchida and Iwamoto, 2014). Sacral nerve stimulation also improves fundic accommodation in rats *via* a spinal-afferent and vagal-efferent pathway (Ye et al., 2020). Trinitrobenzene sulphonic acid-induced colitis in rats is associated with delayed GE, mediated by a neuronal pathway since the pelvic nerve section reverses the delayed emptying (De Schepper et al., 2007). Finally, mice are more sensitive to the inhibition of upper GI transit by loperamide, a mu-

opioid receptor agonist, 28 days after mustard oil-induced colitis compared to control mice that did not have chemical colitis (Kimball et al., 2005). In humans, healthy subjects who voluntarily inhibit defaecation for four days develop delayed GE, a phenomenon known as the “colo-gastric brake” (Tjeerdsma et al., 1993). Rectal distension affects the postprandial release of digestive hormones that regulate GI motility (van Hoek et al., 2000) and inhibits GE (Coremans et al., 2004) in healthy subjects. It has also been shown that the normalisation of intestinal transit in constipated children suffering from gastroparesis improves GE (Boccia et al., 2008). Adult patients with slow-transit constipation have impaired fundic accommodation (Penning et al., 2001) and display delayed GE, which can be reversed in a subset following colectomy (Hemingway and Finlay, 2000). Functional dyspepsia is encountered in about 40% of patients with refractory chronic constipation in tertiary care (Boyd et al., 2023).

Conversely, links between upper GI processes and bowel physiology are also described. For example, there is an immunological crosstalk between the upper and lower GI tract in mice, as shown by *H. pylori* infection that represses the lower GI tract Th17 response to bacterially-induced colitis (Higgins et al., 2011). In this study, *H. pylori*/*Salmonella typhimurium* co-infection decreased inflammation in the caecum and the stomach. A gastro-colic reflex has been described in humans, with increased colonic motility following a meal (Rao et al., 2000). Triggers for this gastro-colonic response include gastric distention, caloric intake and fat intake (Dorfman et al., 2022). The vagus nerve and serotonin mediate this response. Indeed, ondansetron, a selective 5-hydroxytryptamine 3 (5-HT₃) receptor antagonist, inhibits this postprandial gastrocolonic response (von der Ohe et al., 1994).

Besides these physiological links, visceral sensitivity crosstalks have been described in animal models, and clinical situations could suggest similar phenomena in humans.

Evidence in animals

Animal models involving acute or chronic inflammation of the stomach or the colon and assessing visceral sensitivity of the colon or the stomach, respectively, could determine a possible cross-sensitisation between these two organs.

From stomach to colon

No animal model investigated whether a gastric insult could induce colonic hypersensitivity.

From colon to stomach

Neonatal colonic inflammation induced by intrarectal administration of TNBS (130 mg/kg, 10% ethanol) at Day 10 post-natal in male Sprague-Dawley rats causes an increase in basal plasma norepinephrine, which contributes to gastric hypersensitivity 5-8 weeks later, through the upregulation of NGF expression in the gastric fundus (Li et al., 2016). The same group showed that colonic inflammation upregulates tyrosine hydroxylase in the coeliac ganglion, which upregulates the release of norepinephrine in the fundic muscularis. This increased norepinephrine release from the sympathetic nerve terminals upregulates NGF, which proportionately increases the visceromotor response (VMR) to gastric distention in those rats later in life (Winston and Sarna, 2016). Apart from increasing the sympathetic nervous system activity of those rats, neonatal colonic inflammation also increases anxiety-like behaviour in adult life (Winston and Sarna, 2016). To our knowledge, however, the possibility that chemical colitis could induce gastric hypersensitivity has never been studied in adult rodents. Furthermore, a neurological mechanism has yet to be investigated, although rodents' vagus nerve innervates the stomach and the entire colon. However, neurons co-innervating the stomach and the right-sided colon have not been described, but spinal trans-segmental and supra-spinal mechanisms could also be involved.

Evidence in humans

Some clinical situations are associated with acute or chronic inflammation of the stomach or the colon and could give indications of a possible cross-sensitisation between these two organs in humans. However, no data on visceral sensitivity is available in these situations; only complaints suggestive of visceral hypersensitivity of the upper or lower GI tract are reported in the literature.

From stomach to colon

Among patients diagnosed with IBS in primary care in Germany, 21% had a diagnosis of "gastritis/duodenitis" (coded K29 in the ICD-10) in the 12 months before their diagnosis (Loosen et al., 2022).

A nationwide study in Taiwan found that *H. pylori* infection was associated with an increased risk of IBS (OR 3.11 [95% CI: 1.93-5.00]) (Liang et al., 2020). Results from meta-analyses are, however, contradictory: one meta-analysis confirmed this association (Wang et al., 2021), while others didn't (Ng et al., 2019, Kim et al., 2020, Li et al., 2020). Conversely, *H. pylori* therapy was associated with a reduced risk of IBS in the Taiwanese nationwide study (OR 0.46 [95% CI: 0.15-0.96]) (Liang et al., 2020); two meta-analyses have confirmed that successful *H. pylori* eradication is associated with improvement in IBS symptoms (Xiong et al., 2020, Wang et al., 2021).

From colon to stomach

About 20% of patients with **inflammatory bowel diseases** (IBD), Crohn's disease and ulcerative colitis (UC), experience persistent symptoms (pain, diarrhoea, etc.) despite remission of the disease, which is defined as healing of gut inflammation (Casellas et al., 2012). A few studies have shown delayed GE in some patients with inactive and nonobstructive Crohn's disease compared with healthy controls (Annese et al., 1995). Delayed GE is associated with dyspeptic complaints in patients with inactive Crohn's disease (Nobrega et al., 2012). Delayed GE could be partly mediated by an increased release of cholecystokinin (Keller et al., 2009). However, an effect of past gastro-duodenal involvement cannot be ruled out even if the disease was inactive at the time of those studies since Crohn's disease can affect the entire gut. Nevertheless, the perception of infusions of acid or lipid in the duodenum is not different in patients with Crohn's disease or ulcerative colitis in remission compared to healthy individuals (Minderhoud et al., 2006). In quiescent ulcerative colitis, which only affects the colorectum, the prevalence of FD-like symptoms was no different from its prevalence in healthy volunteers in a Japanese study (5.2 vs 6.7%, $p > 0.05$) (Kotani et al., 2020). However, 77.8% of these patients with FD-like symptoms displayed concomitant IBS-like symptoms.

Diverticulosis of the colon is very common in the Western population and is not a disease unless symptoms related to the diverticula develop (Schultz et al., 2020). **Diverticular disease** encompasses symptomatic uncomplicated diverticular

disease (SUDD), diverticulitis (acute/chronic and uncomplicated/complicated) and diverticular bleeding. SUDD is a controversial entity which could represent the overlap between IBS and diverticulosis of the colon. No data is available on the prevalence of FD-like symptoms following acute diverticulitis. However, 6.7% of the patients with SUDD have FD-like symptoms (Annibale et al., 2012). Even in the absence of a control group, the low prevalence of dyspeptic complaints suggests that it is similar to that of the general population. However, the proportion of patients with FD-like symptoms was significantly higher in a group with prolonged abdominal pain (> 24 hours) compared to other patients (13.5 vs 4.6%, $p < 0.0085$) (Annibale et al., 2012).

1.8. Summary

Functional dyspepsia is a complex disorder involving dysregulation of the signalling between the gut and the CNS. The disorder has been associated with numerous comorbidities and overlap syndromes. The impact and pathophysiology of these associations still need to be better understood. Cross-organ visceral sensitisation is implicated in the overlap between functional disorders, particularly those arising from the organs of the pelvis. The physiological reactions and some clinical situations associated with acute or chronic inflammation of the stomach or colon (increased risk of IBS in patients infected with *H. pylori*, for example) suggest a link between the upper and lower digestive tracts in humans. The possibility of cross-organ sensitisation between the stomach and colon, however, is unknown.



Chapter 2 RESEARCH OBJECTIVES

OUR PROJECT AIMED TO STUDY comorbidities and overlap syndromes associated with FD in adults at both clinical and experimental levels. Indeed, they have mainly been studied in IBS among DBGI (Whitehead et al., 2002, Riedl et al., 2008, Shiha and Aziz, 2021).

We assessed current knowledge about comorbidities in FD by performing a systematic review of the medical literature, hypothesising that gaps in knowledge would be identified. This could help design further studies and give clues to underlying pathophysiology.

In the clinical part, we first focused on comorbidities associated with FD and involving only one organ (sleep in FD, nausea/vomiting in FD, and the link between GE and symptoms). We considered sleep disorders of particular interest because they allowed us to assess the effect of comorbidity on FD. We hypothesised that sleep alterations would be associated with lower QoL in the disorder. Since symptoms define FD, it is paramount to use clear symptoms for a correct diagnosis. Successive Rome criteria have changed the place of nausea and vomiting in the dyspepsia spectrum of related symptoms. We decided to compare patients with FD alone, CNVS alone, and FD+CNVS overlap, with the hypothesis that patients with both FD and CNVS criteria would be closer to those with FD alone than with CNVS alone. We then assessed factors possibly linked with symptoms in dyspepsia; we focussed on GE due to data availability. We hypothesised that GE was not a significant determinant of symptoms, as already reported, but it would be a major determinant in patients with more severely delayed emptying. Secondly, we focussed on overlaps with disorders involving other organs (bowel and urinary bladder). No data was available on the overlap with BPS in FD in the literature. We hypothesised that some patients would suffer from BPS and that overlaps with other disorders would be associated with increased disease severity and poorer QoL.

In the experimental part, we first analysed the data from a previous laboratory study concerning bladder-colon interactions. Similarly to the cross-sensitisation model in mice between the bladder and the colon, we decided to examine whether the overlap between FD and IBS, one of the most common overlaps between DGBI, could be partially explained by a similar phenomenon

Chapter 2

between the lower and the upper GI tracts. We aimed to develop a rodent model of cross-organ visceral sensitisation between the colon and the stomach and, if applicable, to assess the mechanisms involved in the development of this cross-organ visceral hypersensitivity. We hypothesised that colon-stomach cross-sensitisation was possible in the rats due to the shared innervation of the stomach and the proximal colon, and that this cross-sensitisation would involve the microglia.



Chapter 3 ARTICLE 1. SYSTEMATIC REVIEW WITH META-ANALYSIS OF COMORBIDITIES AND OVERLAP SYNDROMES IN FUNCTIONAL DYSPEPSIA

3.1. Introductory paragraph

Articulation with previous projects

We reviewed knowledge about comorbidities and overlap syndromes in FD.

What is already known?

Evidence-based associations between FD and different comorbidities and overlap syndromes are only available for specific comorbidities (e.g., GORD, depression, etc.).

Research question

- Which comorbidities and overlap syndromes are already reported in FD?

Aims

- Build an overview of the evidence-based associations between FD and different comorbidities and overlap syndromes.
- Identify gaps in knowledge about comorbidities in FD.

Methodology

- Systematic review
- Database used: MEDLINE (PubMed®)
- Timeframe: until February 2022
- Synthesis of the association between FD and different comorbidities

My contribution

I performed the systematic review (study selection and data acquisition) and drafted the manuscript.

3.2. Title page

Complete title

Comorbidities and overlap syndromes in functional dyspepsia: a systematic review with meta-analysis

Short title

Systematic review of comorbidities in functional dyspepsia

Authors' names

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3.3. Abstract

Different comorbidities have been reported in patients with functional dyspepsia: organic diseases (*H. pylori* gastritis, diabetes mellitus, lactose intolerance, etc.), other functional gastrointestinal disorders (gastro-oesophageal reflux disease, irritable bowel syndrome, etc.), non-gastrointestinal functional somatic disorders (fibromyalgia, chronic fatigue syndrome, migraine, etc.) and psychological factors (anxiety, depression, sleep disorders, etc.). We aimed to build an overview of the evidence-based associations between functional dyspepsia and different comorbidities. We performed a systematic review using MEDLINE (PubMed®) until February 2022: 5,131 references were identified, of which 250 were kept for analysis. This review article discusses the evidence linking different comorbidities with functional dyspepsia, especially for those in which a control group was available.

3.4. Introduction

FUNCTIONAL GI DISORDERS, NOW CALLED DGBI, are a group of digestive disorders characterised by chronic (> six months) GI complaints without any organic cause found by medical investigations. Functional dyspepsia is among the most prevalent DGBI. According to Rome IV criteria (Stanghellini et al., 2016), FD is characterised by at least one of the following upper digestive symptoms: postprandial fullness, early satiation, epigastric pain or burning, lasting for more than six months and without organic disorder explaining them. The beginning of the symptoms needs to be at least six months ahead. The disease can be subdivided into post-prandial distress syndrome, characterised by meal-related symptoms, and EPS, characterised by meal-unrelated symptoms. Functional dyspepsia affects about 10% of the general population in the Western world (Aziz et al., 2018a).

Functional dyspepsia frequently overlaps with GORD or IBS, two highly prevalent DGBI. Overlap syndromes are associated with impaired QoL, more severe symptoms and worse outcomes in dyspepsia (Gwee et al., 2008). Furthermore, patients with FD regularly present other comorbidities, like anxiety and depression. The awareness of the importance of taking them into account is increasing over time, as exemplified by the 2016 recommendation to assess overlaps, comorbidities and disease modifiers in the design of clinical trials concerning FD (Irvine et al., 2016).

Our aim was to build a systematic overview of the evidence-based associations between FD and different comorbidities and overlap syndromes. Discussing the pathophysiology of overlaps is out of the scope of this review.

3.5. Methods

The systematic review was carried out according to the guidelines recommended by the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) (Page et al., 2021) and the *Guidelines for Accurate and Transparent Health Estimates Reporting* (GATHER) groups (Stevens et al., 2016). The review was not prospectively registered because it did not include a health-related outcome. The literature search, study selection and data extraction were performed by a single investigator (Fabien Wuestenberghs).

Search strategy

A comprehensive medical literature search using MEDLINE (PubMed®) database was performed without date restriction to identify original articles involving adult patients suffering from FD in which comorbidities, overlap syndromes or disease modifiers were mentioned, published in English and with the complete reports available. The following terms were used for the search: “functional dyspepsia” OR^a “epigastric pain syndrome” OR “postprandial distress syndrome” OR “ulcer-like dyspepsia” OR “dysmotility-like dyspepsia” OR “non-ulcer dyspepsia” OR “nonulcer dyspepsia” (all as free text terms in the title and the abstract). The search was carried out on February 23, 2022. The search results were imported to Endnote software (version 20.2.1) and stored to screen titles and abstracts.

Selection criteria

Titles and abstracts from identified studies were screened for suitability, with those appearing relevant being collected and analysed in detail within their full text. The diagnosis of FD relied on clinical diagnosis with negative workup or symptom-based diagnostic criteria, according to Rome (Ford et al., 2017). The review was limited to original articles. We excluded case studies, review articles, systematic reviews with or without meta-analyses, pathophysiological studies, editorials, letters to the editor and conference papers, articles not written in English or without available full text, studies with sample size < 50 participants, and studies involving children (age below 18 years old). We also excluded studies in which only one FD subtype was represented, cohorts published more than once (only the one reported the most recently was used), and if only scores were available and not diagnoses (especially for psychological factors). We only included observational studies (especially population-based cohorts but also others if involving consecutive patients to reduce selection bias); RCT were excluded, except two which included successive patients.

^a "OR" in this paragraph is the boolean operator meaning that there is at least one true.

Data extraction & quality assessment

Extracted data were first author name, year of publication, investigations (questionnaire, endoscopy, other tests), sample size, setting (population-based, primary/secondary/tertiary care), findings on comorbidities (especially prevalence in the cohort) and criteria used for FD diagnosis. Data concerning population-based cohorts were reported separately since random population-based samples are more representative of the prevalence of comorbidities in FD due to the absence of referral bias. Reference lists of selected articles were screened to find new relevant studies. Quality assessment of the included studies was performed using the *Grades of Recommendation, Assessment, Development and Evaluation* (GRADE) approach (Guyatt et al., 2008, Guyatt et al., 2011) adapted to observational studies (Edwards et al., 2017) as shown in Addendum 1. Supplementary data for Article 1 (Supplementary Table 1.1).

Data analysis & synthesis

The reported prevalence range for each comorbidity was summarised for population-based and non-population-based studies and synthesised. The results were at the origin of a narrative synthesis on the topic. For the subgroup of studies involving a control group, raw data of the prevalences of comorbidities has been extracted to calculate OR. A synthesis of OR was obtained for comorbidities assessed in at least two studies. (Pooled) OR were calculated using Fisher's exact test (or the Woolf logit interval in case of large samples). A Forrest plot with sub-analyses for patients from the general population and for healthcare-seeking patients was performed for IBS comorbidity. The data were analysed using GraphPad Prism version 9.5.1 (733) for Windows (GraphPad Software Inc, San Diego, CA, USA, www.graphpad.com).

3.6. Results

We identified 5,131 records from MEDLINE (PubMed®). We excluded 586 articles before screening (577 non-English and nine book chapters). We excluded 4,191 articles during screening based on the content of the abstract (199 basic science studies, 25 case reports, 205 paediatric studies, 910 biased cohorts, 22

guidelines, 453 studies about *H. pylori*, 106 letters and editorials, one non-English, 410 not concerning FD, seven pathophysiological studies, 31 protocols, 514 RCT, 1,057 reviews, 14 other non-research articles, 182 systematic reviews or meta-analyses, 55 for different reasons and four full-texts not available). Full-text articles assessed for eligibility were, therefore, 350. We excluded 99 papers (27 not concerning FD, 71 without data on comorbidities, one concerning only one FD subtype and one from which we were unable to extract data). In the end, we included 250 articles for the final analysis. The flowchart of the selection of the articles according to PRISMA guidelines is shown in Figure 3.1. Among those 250 articles, 67 contained data to calculate or extract OR for specific comorbidities in FD patients compared to controls.

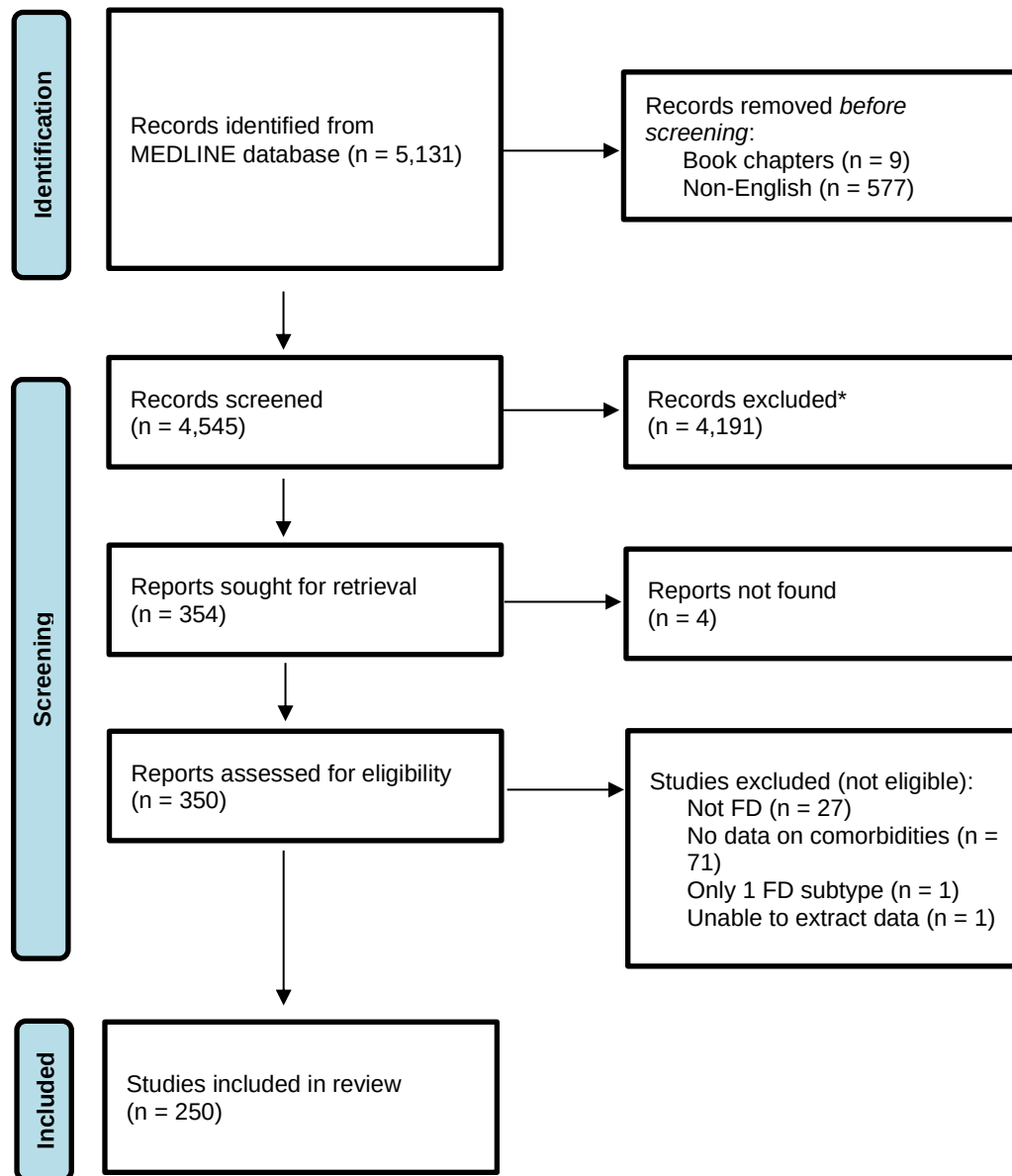


Figure 3.1. PRISMA flow diagram

* animals n = 199; case reports n = 25, children n = 205, FD but biased cohort n = 910, guidelines n = 22, *H. pylori* n = 453, letters & editorials n = 106, not an original article n = 14, non-English n = 1, not FD n = 410, pathophysiology n = 7, protocols n

= 31, RCT $n = 514$, reviews $n = 1,057$, systematic reviews & meta-analysis $n = 182$, others $n = 55$.

FD: functional dyspepsia.

Numerous overlap syndromes and comorbidities have been reported in FD patients. Among the 250 articles included, raw data were available in 176 articles. Among the 176 articles with actionable data, 105 (59.7%) involved investigated patients. Controls were present in 101 studies (57.4%). Investigations took place in different settings: primary care (4.0%), secondary care (14.8%), tertiary care (44.9%), workers/students/health check-ups (11.4%) or the general population (25.0%). Functional dyspepsia was diagnosed according to Rome criteria (whatever the iteration) in 74.4% of the cases (131 studies).

Categorising “comorbidities” associated with FD is not consensual. We propose to classify them arbitrarily into four groups for this review: (1) overlaps with organic diseases (*H. pylori* infection, diabetes mellitus, gastroparesis, etc.); (2) overlaps with other DGBI (GOR, IBS, etc.); overlaps with non-GI functional somatic disorders belonging to “central sensitivity syndromes” (fibromyalgia, CFS, migraine, BPS, etc.) and psychological factors (anxiety, depression, stress, somatisation, sleep disorders, etc.).

Details of extracted data from all articles included in the review are shown in Supplementary Table 1.2.

Overlaps with organic diseases

The prevalences of organic diseases in FD patients are shown in Table 3.1. Organic diseases for which prevalences were available in more than one study are *H. pylori* gastritis (0-68.4%), SIBO (0-71.4%), diabetes mellitus (9.2-28.9%), erosive oesophagitis (4.2-25.8%), essential hypertension (14.8-37.3%), asthma (14.9-22.0%), coeliac disease (1.3-7.1%), self-reported wheat sensitivity (23.8-25.3%), atrophic gastritis (31.8-40.8%), JHS (42.6-59.2%), gallstones (4.4-9.2%), pancreatic exocrine dysfunction (27.3-71.9%) and early chronic pancreatitis (11.3-24.5%). The prevalence of other organic diseases has been reported only once (acute bronchitis, hyperlipidaemia, inter-vertebral disc disorders, excessive duodeno-gastric reflux, pancreatic enzyme abnormalities, angina, myocardial infarction, osteoporosis, osteoarthritis, spine arthritis, atopy, eczema, hay fever/rhinitis,

allergic conjunctivitis, chronic obstructive pulmonary disease, diverticular disease, disk hernia, ovarian cysts, enlarged prostate, pulmonary embolism ± deep venous thrombosis, *Giardia lamblia* infection, nutcracker oesophagus, diffuse oesophageal spasm, nonspecific oesophageal motor disorders, erosive gastritis, gallbladder dyskinesia, superior mesenteric artery syndrome, cirrhosis, stroke, systemic sclerosis, psoriasis, rheumatoid arthritis, food allergy, pollen allergy, animal allergy, lactose malabsorption, adult-type hypolactasia (genotype), fructose malabsorption, sorbitol malabsorption, fissured tongue and hiatus hernia).

Table 3.1. Prevalence of organic diseases overlapping with functional dyspepsia.

Comorbidity	Prevalence in population-based cohorts	Prevalence in non-population-based cohorts	Overall prevalence among all studies	References
Helicobacter pylori gastritis	15.2-56.1%	0.0-68.4%	0.0-68.4%	(Fang et al., 2015) (Fujikawa et al., 2017) (Futagami et al., 2013a) (Gathaiya et al., 2009) (Hammer, 2018) (Hashimoto et al., 2017) (Hu et al., 2021) (Jung et al., 2016) (Kawamura et al., 2001) (Kawanishi et al., 2017) (Kim et al., 2014, Kim et al., 2018a) (Kinoshita and Chiba, 2011) (Lee et al., 2013) (Locke et al., 2000) (Lorena et al., 2002a) (Lorena et al., 2004) (Mahadeva and Goh, 2011) (Nam et al., 2021) (Pajala et al., 2012) (Perri et al., 1998) (Stone et al., 1998) (Tack et al., 2001) (Takamori et al., 2007) (Talley et al., 2007) (Tse et al., 2010) (Tziatzios et al., 2021) (Vakil et al., 2016b) (Wilhelmsen et al., 1995) (Xiao et al., 2010) (Zagari et al., 2010)
Diabetes mellitus	9.2-27.3%	10.2-28.9%	9.2-28.9%	(Ebling et al., 2016, Kawanishi et al., 2017) (Koloski et al., 2019) (Lu et al., 2005) (Park et al., 2021) (Tse et al., 2010)
Acute bronchitis	/	8.8%	8.8%	(Brook et al., 2012)
Hyperlipidaemia	/	21.2%	21.2%	(Brook et al., 2012)
Essential hypertension	21.3-22.9%	14.8-37.3%	14.8-37.3%	(Brook et al., 2012) (Gudlaugsdottir et al., 2002) (Lu et al., 2005) (Park et al., 2021) (Tse et al., 2010)
Inter-vertebral disc disorders	/	22.1%	22.1%	(Brook et al., 2012)

Systematic review of comorbidities

Small intestinal bacterial overgrowth	/	0.0-56.5%	0.0-56.5%	(Chojnacki et al., 2020) (Chuah et al., 2022) (Costa et al., 2012, Kawanishi et al., 2017, Lorena et al., 2002a) (Mishkin et al., 1997) (Shimura et al., 2016) (Tziatzios et al., 2021)
Excessive duodenogastric reflux	/	44.3%	44.3%	(Fein et al., 2002)
Joint hypermobility syndrome/ Ehlers-Danlos syndrome- hypermobility type	/	42.6-59.2%	42.6-59.2%	(Fikree et al., 2015) (Fikree et al., 2017)
Any autoimmune disorder	4.8%	/	4.8%	(Ford et al., 2014)
Pancreatic exocrine dysfunction	/	27.3-71.9%	27.3-71.9%	(Fujikawa et al., 2017)Smith et al. (1991)
Pancreatic enzyme abnormalities	/	28.9%	28.9%	(Hashimoto et al., 2017)
Early chronic pancreatitis	/	11.3-24.5%	11.3-24.5%	(Hashimoto et al., 2017) (Lariño-Noia et al., 2018)
Angina	6.6%	/	6.6%	(Garcia-Etxebarria et al., 2022)
Gallstones	4.4-9.2%	4.4-4.7%	4.4-9.2%	(Garcia-Etxebarria et al., 2022) (Lu et al., 2005) (Talley et al., 1986) (Talley and Piper, 1986)
Myocardial infarction	3.9%	/	3.9%	(Garcia-Etxebarria et al., 2022)
Osteoporosis	3.7%	/	3.7%	(Garcia-Etxebarria et al., 2022)
Osteoarthritis	14.8%	/	14.8%	(Garcia-Etxebarria et al., 2022)
Spine arthritis	1.8%	/	1.8%	(Garcia-Etxebarria et al., 2022)
Atopy	/	41.8%	41.8%	(Jones et al., 2014)
Eczema	/	27.5%	27.5%	(Jones et al., 2014)
Hay fever/rhinitis	/	7.8%	7.8%	(Jones et al., 2014)

Chapter 3

Allergic conjunctivitis	/	3.1%	3.1%	(Jones et al., 2014)
Asthma	16.5-22.0%	14.9%	14.9-22.0%	(Garcia-Etxebarria et al., 2022) (Jones et al., 2014) (Koloski et al., 2019)
Chronic obstructive pulmonary disease	2.3%	/	2.3%	(Garcia-Etxebarria et al., 2022)
Diverticular disease	2.2%	/	2.2%	(Garcia-Etxebarria et al., 2022)
Disk hernia	2.9%	/	2.9%	(Garcia-Etxebarria et al., 2022)
Ovarian cysts	1.8%	/	1.8%	(Garcia-Etxebarria et al., 2022)
Enlarged prostate	2.1%	/	2.1%	(Garcia-Etxebarria et al., 2022)
Pulmonary embolism ± deep venous thrombosis	1.5%	/	1.5%	(Garcia-Etxebarria et al., 2022)
Coeliac disease	2.1%	1.3-7.1%	1.3-7.1%	(Giangreco et al., 2008) (Keshavarz et al., 2010) (Lasa et al., 2017)
Self-reported gluten/wheat sensitivity	23.8-25.3%	/	23.8-25.3%	(Potter et al., 2018) (Potter et al., 2020)
Giardia lamblia infection	/	4.8%	4.8%	(Grazioli et al., 2006)
Nutcracker oesophagus	/	14.1%	14.1%	(Handa et al., 1999)
Diffuse oesophageal spasm	/	5.6%	5.6%	(Handa et al., 1999)
Nonspecific oesophageal motor disorders	/	40.8%	40.8%	(Handa et al., 1999)
Erosive oesophagitis	/	4.2-25.8%	4.2-25.8%	(Jung et al., 2016) (Lee et al., 2013) (Mochizuki et al., 2018) (Noh et al., 2010) (Tziatzios et al., 2021)
Erosive gastritis	/	5.3%	5.3%	(Lee et al., 2013)
Gallbladder dyskinesia	/	46.7%	46.7%	(Jung et al., 2017)

Systematic review of comorbidities

Superior mesenteric artery syndrome	/	10.9%	10.9%	(Kawanishi et al., 2017)
Cirrhosis	/	10.9%	10.9%	(Kawanishi et al., 2017)
Stroke	/	8.7%	8.7%	(Kawanishi et al., 2017)
Atrophic gastritis	/	31.8-40.8%	31.8-40.8%	(Kim et al., 2014, Kim et al., 2018a)
Systemic sclerosis	0.3%	/	0.3%	(Koloski et al., 2019)
Psoriasis	5.6%	/	5.6%	(Koloski et al., 2019)
Rheumatoid arthritis	8.5%	/	8.5%	(Koloski et al., 2019)
Food allergy	10.9%	/	10.9%	(Koloski et al., 2019)
Pollen allergy	9.9%	/	9.9%	(Koloski et al., 2019)
Animal allergy	4.6%	/	4.6%	(Koloski et al., 2019)
Lactose malabsorption	/	55.6%	55.6%	(Mishkin et al., 1997)
adult-type hypolactasia (genotype)	/	44.7%	44.7%	(Wortmann et al., 2018)
Fructose malabsorption	/	52.9%	52.9%	(Mishkin et al., 1997)
Sorbitol malabsorption	/	57.7%	57.7%	(Mishkin et al., 1997)
Fissured tongue	/	78.9%	78.9%	(Song et al., 2019)
Hiatus hernia	/	27.7%	27.7%	(Vakil et al., 2016b)

Overlaps with other disorders of gut-brain interactions

The prevalences of other DGBI in FD patients are shown in Table 3.2. Disorders of gut-brain interactions for which prevalences were available in more than one study are IBS (1.8-80.2%), GORD/heartburn (9.0-62.7%), functional heartburn (6.3-62.8%), belching (6.9-59.0%), functional diarrhoea (0.5-22.6%), functional constipation (12.8-39.0%), chronic unexplained nausea (3.4-5.5%), vomiting (4.2-33.1%), and unspecified functional bowel disorder (3.4-57.5%). The prevalence of other DGBI has been reported only once (CNVS, CVS, functional defecation disorder, globus, functional abdominal pain syndrome, functional biliary sphincter of Oddi disorder, functional dysphagia, functional faecal incontinence, levator ani syndrome, rumination syndrome, abdominal bloating and aerophagy).

Table 3.2. Prevalence of other disorders of gut-brain interactions overlapping with functional dyspepsia.

Comorbidity	Prevalence in population-based cohorts	Prevalence in non-population-based cohorts	Overall prevalence among all studies	References
Gastro-oesophageal reflux/heartburn	9.4-62.7%	9.0-55.1% (20.0-35.0% with abnormal pH profile)	9.0-62.7% (20.0-35.0% with abnormal pH profile)	(Aro et al., 2009) (Aro et al., 2015) (Carbone et al., 2020) (Fujiwara et al., 2011) (Futagami et al., 2013b, 2013c) (Garcia-Etxebarria et al., 2022) (Gerson and Triadafilopoulos, 2005) (Hammer, 2018) (Herrick et al., 2015) (Hori et al., 2009) (Jarbøl et al., 2017) (Kaji et al., 2010) (Matsuzaki et al., 2018) (Min et al., 2014) (Mori et al., 2017) (Morito et al., 2014, 2021) (Noh et al., 2010) (Ohara et al., 2011) (Olmos et al., 2006) (Park et al., 2021, 2022) (Perri et al., 1998) (Rasmussen et al., 2015) (Shaib and El-Serag, 2004) (Shimpuku et al., 2014) (Small et al., 1995) (Stanghellini et al., 1999) (Tack et al., 2005) (Talley et al., 1986) (Talley and Piper, 1986) (Talley et al., 1990) (Tse et al., 2010) (Vakil et al., 2016a) (Welén et al., 2008) (Xiao et al., 2010) (Zagari et al., 2010) (Van Oudenhove et al., 2016a)
Irritable bowel syndrome	1.8-80.2%	2.8-76.7%	1.8-80.2%	(Agréus et al., 1995) (Aro et al., 2015) (Aziz et al., 2018a) (Caballero-Plasencia et al., 1999) (Choi et al., 2017) (Corsetti et al., 2004) (Crean et al., 1994) (Dibaise et al., 2016a) al., 2013) (Fang et al., 2015) (Fass et al., 1998) (Fass et al., 2000, Fujiwara et al., 2011, Futagami et al., 2013b, 2013c) (Garcia-Etxebarria et al., 2022) (Ghoshal and Singh, 2017) (Goyal et al., 2020) (Hammer, 2018) (Herrick et al., 2015) (Hori et al., 2009) (Jang et al., 2016) (Jarbøl et al., 2017) (Jones et al., 2013a) (Jung et al., 2016) (Kaji et al., 2010)

Chapter 3

				(Kim et al., 2018b) (Koloski et al., 2003) (Koloski et al., 2005a) (Koloski et al., 2005b) (Koloski et al., 2020) (Le Pluart et al., 2015) (Lim et al., 2017) (Locke et al., 2000) (Lu et al., 2005) (Ly et al., 2015) (Matsuzaki et al., 2012, Matsuzaki et al., 2018) (Min et al., 2014) (Minocha et al., 2006, Mishkin et al., 1997) (Miwa, 2012) (Morito et al., 2014, Nakajima et al., 2010) (Nam et al., 2021) (Nwokediuko et al., 2012) (Olafsdottir et al., 2010) (Oshima et al., 2015) (Oshima et al., 2021, Pajala et al., 2005, Pajala et al., 2012) (Palsson et al., 2016) (Park et al., 2011) (Perveen et al., 2014) (Pittock et al., 2011) (Perri et al., 1998) (Persson et al., 2015) (Rahman et al., 2020, Rasmussen et al., 2015) (Schindler et al., 2019) (Shimpuku et al., 2014, Shimura et al., 2016) (Sorouri et al., 2010) (Stanghellini et al., 1999) (Steinsvik et al., 2020) (Talley et al., 1986) (Talley and Piper, 1986) (Talley et al., 1990) (Talley et al., 2019, Tse et al., 2010) (Vakil et al., 2016a) (Van Oudenhove et al., 2008) (Van Oudenhove et al., 2011a) (Van Oudenhove et al., 2011c) (Van Oudenhove et al., 2016a) (von Wulffen et al., 2019) (Vu et al., 2014) (Wang et al., 2008a) (Welén et al., 2008) (Wensaas et al., 2016) (Wilder-Smith et al., 2018) (Wu et al., 2013) (Xiong et al., 2014, Zagari et al., 2010)
Belching	28.8-36.1%	6.9-59.0%	6.9-59.0%	(Aro et al., 2009) (Carbone et al., 2020) (Hu et al., 2021) (Nakajima et al., 2010) (Park et al., 2011)
Functional heartburn	12.0%	6.3-62.8%	6.3-62.8%	(Aziz et al., 2018a) (Jang et al., 2016) (Park et al., 2011) (Wu et al., 2013)
Vomiting	4.2%	10.1-33.1%	4.2-33.1%	(Brook et al., 2012) (Corsetti et al., 2004) (Min et al., 2014) (Nam et al., 2021) (Stanghellini et al., 1999) (Tack et al., 2001) (Tack et al., 2005) (Vanheel et al., 2013)

Systematic review of comorbidities

Functional constipation	17.0-17.1%	12.8-39.0%	12.8-39.0%	(Hammer and Talley, 2006, Jang et al., 2016) (Le Pluart et al., 2015) (Nakajima et al., 2010) (Palsson et al., 2016) (Sorouri et al., 2010, Talley et al., 1990) (Vakil et al., 2016a)
Functional diarrhoea	1.2%	0.5-22.6%	0.5-22.6%	(Hammer and Talley, 2006, Le Pluart et al., 2015, Nakajima et al., 2010) (Sorouri et al., 2010) (Talley et al., 1990)
Chronic nausea and vomiting syndrome	/	82.4%	82.4%	(Jehangir and Parkman, 2018)
Chronic unexplained nausea	/	3.4-5.5%	3.4-5.5%	(Jung et al., 2019) (Nakajima et al., 2010)
Cyclic vomiting syndrome	/	6.9%	6.9%	(Nakajima et al., 2010)
Functional defecation disorder	/	6.9%	6.9%	(Nakajima et al., 2010)
Globus	/	6.9%	6.9%	(Nakajima et al., 2010)
Functional abdominal pain syndrome	/	3.4%	3.4%	(Nakajima et al., 2010)
Functional biliary sphincter of Oddi disorder	/	3.4%	3.4%	(Nakajima et al., 2010)
Functional dysphagia	/	3.4%	3.4%	(Nakajima et al., 2010)
Functional faecal incontinence	/	3.4%	3.4%	(Nakajima et al., 2010)
Levator ani syndrome	/	3.4%	3.4%	(Nakajima et al., 2010)
Rumination syndrome	/	3.4%	3.4%	(Nakajima et al., 2010)
Unspecified functional bowel disorder	57.5%	3.4%	3.4-57.5%	(Nakajima et al., 2010) (Sorouri et al., 2010)
Abdominal bloating	/	65.7%	65.7%	(Ryu et al., 2016)
Aerophagy	/	27.6%	27.6%	(Talley et al., 1986)

Overlaps between different DGBI are frequent: among individuals meeting the criteria of one or more of the conditions GORD, FD and IBS, 30.7% had an overlap between two or all three conditions (Rasmussen et al., 2015). In particular, FD frequently overlaps with other DGBI, especially GORD or IBS, found in 24 and 14% of Rome II-based dyspeptic subjects in a Korean study (Lee et al., 2009). In a cross-sectional study of Japanese workers, overlaps with GORD and/or IBS were also found in 47.6% of FD patients (Kaji et al., 2010). These overlaps seem to occur predominantly in anxious people, anxiety being significantly associated with overlap with GORD and IBS in FD (OR 3.19 [95% CI: 1.33-7.63]) compared with FD alone in the Korean population (Lee et al., 2009).

Overlaps with non-gastrointestinal functional somatic syndromes

The prevalences of non-GI functional somatic syndromes in FD patients are shown in Table 3.3. Such disorders for which prevalences were available in more than one study are migraine (5.5-68.0%), CFS (39.4-43.4%), overactive bladder (18.9-20.5%), and low back pain (3.3-80.8%). The prevalence of headaches has been reported only once.

Table 3.3. Prevalence of non-gastrointestinal functional somatic syndromes overlapping with functional dyspepsia.

Comorbidity	Prevalence in population-based cohorts	Prevalence in non-population-based cohorts	Overall prevalence among all studies	References
Fibromyalgia	/	/	/	
Chronic fatigue syndrome	43.4%	39.4%	39.4-43.4%	(Jones et al., 2013a) (Persson et al., 2015) (Van Oudenhove et al., 2011c)
Migraine	5.5%	15.0-68.0%	5.5-68.0%	(Di Stefano et al., 2019, Garcia-Etxebarria et al., 2022) (Meucci et al., 2005)
Headache, including migraine	/	10.6%	10.6%	(Brook et al., 2012)
Bladder pain syndrome	/	/	/	
Overactive bladder	18.9%	20.5%	18.9-20.5%	(Matsuzaki et al., 2012) (Persson et al., 2015)
Low back pain	3.3%	80.8%	3.3-80.8%	(Garcia-Etxebarria et al., 2022) (Gracie et al., 2015)

Several pain disorders have been associated with DGBI, with heterogeneous nomenclature used in the literature ("somatoform disorders", "functional pain syndromes", "functional somatic syndromes", "central sensitivity syndromes", etc.) (Yunus, 2007, Petersen et al., 2020). It is a group of disorders without organic abnormalities that are likely to explain their symptoms and characterised by central sensitisation (increased excitability of neurons involved in central nociceptive pathways in response to painful or non-painful stimuli, manifesting clinically as hyperalgesia and allodynia respectively) (Woolf, 2011).

Overlaps with psychological factors

The prevalences of psychological factors in FD patients are shown in Table 3.4. Psychological factors for which prevalences were available in more than one study are depression (4.0-100.0%), anxiety (1.7-71.2%), sleep disorders (31.1-93.1%), panic disorder (0-71.2%), generalised anxiety disorder (0-26.2%), somatisation (2.4-92.5%), stress (45.0-69.0%), stressful life events (34.3-83.8%), sexual abuse (1.8-21.4%), physical abuse (7.8-13.6%), insomnia (44.5-53.6%), eating disorder (0-7.0%), PTSD (0-1.4%), personality disorder (4.1-8.0%), hypochondriasis (0-8.1%), dysthymia (0-12.7%), agoraphobia (11.1-11.9%), social phobia (0-11.1%), specific phobia (2.4-38.9%), obsessive-compulsive disorder (0-2.4%), and somatoform disorders (0-10.9%). The prevalence of other psychological factors has been reported only once (excessive daytime sleepiness, sexual dysfunction, conversion disorder, anorexia nervosa, bulimia, bipolar disorder, schizophrenia, adjustment disorders, and substance abuse).

Table 3.4. Prevalence of psychological factors overlapping with functional dyspepsia.

Comorbidity	Prevalence in population-based cohorts	Prevalence in non-population-based cohorts	Overall prevalence among all studies	References
Depression	8.8% 44.4% (in women)	4.0-100.0%	4.0-100.0%	(Dibaise et al., 2016a, Fang et al., 2015) (Filipović et al., 2013) (Fu et al., 2007) (Garcia-Etxebarria et al., 2022) (Handa et al., 1999) (Hartono et al., 2012) (Huang et al., 2020) (Jones et al., 2013a, Jones et al., 2014) (Jonsson et al., 1995) (Kumar et al., 1998) (Liu et al., 2015) (Lorena et al., 2002a) (Lorena et al., 2004) (Ly et al., 2015, Mahadeva and Goh, 2011) (Malt et al., 2000) (Matsuzaki et al., 2018) (Mori et al., 2017) (Park et al., 2021) (Stasi et al., 2017) (Talley et al., 1986) (Tominaga et al., 2007) (Tse et al., 2010) (Van Oudenhove et al., 2008) (Van Oudenhove et al., 2011a) (Vishnar et al., 2000, Welén et al., 2008) (Yuan et al., 2020a) (Zhang et al., 2016)
Anxiety	3.0%	1.7-92.1%	1.7-92.1%	(Aro et al., 2009) (Dibaise et al., 2016a) (Fang et al., 2015) (Fu et al., 2007) (Garcia-Etxebarria et al., 2022) (Handa et al., 1999) (Hartono et al., 2012) (Haug et al., 1994, Huang et al., 2020) (Jones et al., 2014) (Liu et al., 2015) (Lorena et al., 2002a) (Lorena et al., 2004) (Ly et al., 2015, Mahadeva and Goh, 2011) (Matsuzaki et al., 2018) (Mori et al., 2017, Park et al., 2021) (Tominaga et al., 2007)

Chapter 3

				(Tse et al., 2010) (Van Oudenhove et al., 2007, Van Oudenhove et al., 2008) (Vishnar et al., 2000) (Welén et al., 2008) (Yuan et al., 2020a) (Zhang et al., 2016)
Panic disorder	0.0% (women)	0.0-71.2%	0.0-71.2%	(Ghoshal and Singh, 2017, Handa et al., 1999) (Jones et al., 2013a) (Jonsson et al., 1995) (Malt et al., 2000) (Stasi et al., 2017, Tse et al., 2010) (Van Oudenhove et al., 2008) (Van Oudenhove et al., 2011a)
Generalised anxiety disorder	0.0% (women)	4.2-26.2%	0.0-26.2%	(Handa et al., 1999) (Jonsson et al., 1995) (Kumar et al., 1998) (Malt et al., 2000) (Stasi et al., 2017, Tse et al., 2010)
Stress	45.0%	47.8-69.0%	45.0-69.0%	(Haug et al., 1995) (Kinoshita and Chiba, 2011) (Miwa, 2012) (Vishnar et al., 2000)
Somatisation	/	2.4-92.5%	2.4-92.5%	(Dibaise et al., 2016a) (Gracie et al., 2015) (Jonsson et al., 1995) (Stasi et al., 2017) (Tse et al., 2010) (Van Oudenhove et al., 2011a)
Sleep disorders	39.7-75.3%	31.1-93.1%	31.1-93.1%	(Fang et al., 2015) (Fass et al., 2000) (Futagami et al., 2013a) (Ghoshal and Singh, 2017) (Gracie et al., 2015) (Lacy et al., 2011) (Lei et al., 2019b, Lim et al., 2017, Lu et al., 2005) (Matsuzaki et al., 2018) (Morito et al., 2014, Park et al., 2021, Vakil et al., 2016b) (Welén et al., 2008) (Zhao et al., 2018)
Insomnia	/	44.5-53.6%	44.5-53.6%	(Bouchoucha et al., 2018) (Huang et al., 2020)
Excessive daytime sleepiness	33.8%	/	33.8%	(Wu et al., 2017b)
Stressful life events ("life-threatening event")	48.1-55.3%	34.3-83.8%	34.3-83.8%	(Jess and Eldrup, 1994, Koloski et al., 2005b) (Locke et al., 2004b) (Talley and Piper, 1986) (Van Oudenhove et al., 2008)

Systematic review of comorbidities

Sexual abuse	3.4%	1.8-21.4%	1.8-21.4%	(Jones et al., 2013a) (Oshima et al., 2015) (Tse et al., 2010, Van Oudenhove et al., 2011a)
Physical abuse	7.8%	3.5 (adult only)-13.6%	7.8-13.6%	(Jones et al., 2013a) (Oshima et al., 2015) (Van Oudenhove et al., 2011a)
Alexithymia	/	11.7%	11.7%	(Jones et al., 2004)
Sexual dysfunction	/	46.3%	46.3%	(Fass et al., 1998)
Conversion disorder	/	4.2%	4.2%	(Handa et al., 1999)
Eating disorder	/	0.0-7.0%	0.0-7.0%	(Handa et al., 1999, Tse et al., 2010)
Bulimia	/	2.4%	2.4%	(Stasi et al., 2017)
Anorexia nervosa	/	2.4%	2.4%	(Stasi et al., 2017)
Post-traumatic stress disorder	/	0.0-1.4%	0.0-1.4%	(Handa et al., 1999) (Tse et al., 2010)
Psychologic distress	/	38.0-93.1%	38.0-93.1%	(Jones and Maganti, 2004) (Koh et al., 2014) (Lee et al., 2013) (Lim et al., 2017) (Pajala et al., 2005)
Personality disorder	/	4.1-8.0%	4.1-8.0%	(Jonsson et al., 1995) (Kumar et al., 1998)
Hypochondriasis	/	0.0-8.1%	0.0-8.1%	(Kumar et al., 1998) (Tse et al., 2010)
Dysthymia	/	0.0-12.7%	0.0-12.7%	(Kumar et al., 1998) (Stasi et al., 2017) (Tse et al., 2010)
Agoraphobia	11.1% (women)	11.9%	11.1-11.9%	(Malt et al., 2000) (Stasi et al., 2017)
Social phobia	11.1% (women)	0.0-1.8%	0.0-11.1%	(Malt et al., 2000) (Stasi et al., 2017) (Tse et al., 2010)
Specific phobia	38.9% (women)	2.4-10.9%	2.4-38.9%	(Malt et al., 2000) (Stasi et al., 2017) (Tse et al., 2010)
Obsessive-compulsive disorder	/	0.0-2.4%	0.0-2.4%	(Stasi et al., 2017, Tse et al., 2010)
Somatoform disorders	/	0.0-10.9%	0.0-10.9%	(Stasi et al., 2017, Tse et al., 2010)
Bipolar disorder	/	0.0%	0.0%	(Stasi et al., 2017, Tse et al., 2010)

Chapter 3

<i>Schizophrenia & other psychotic disorders</i>	/	0.0%	0.0%	(Tse et al., 2010)
<i>Adjustment disorders</i>	/	1.8%	1.8%	(Tse et al., 2010)
<i>Substance abuse</i>	/	1.8%	1.8%	(Tse et al., 2010)

Associations with psychosocial factors are classically found in FD, including anxiety, depression, somatisation, sleep alterations, etc. Psychological distress, including anxiety and depression, has been reported in 1.7% to 100.0% of FD patients. Psychological factors (depression, abuse history and somatisation) are major determinants of the severity of symptoms in FD (Van Oudenhove et al., 2008).

Associations of comorbidities with FD compared to controls

The OR of the different comorbidities are detailed in Table 3.5.

Table 3.5. Prevalences of different comorbidities in FD patients and controls, with (pooled) odds ratios.

Comorbidity	Prevalences in FD patients	Prevalences in controls	Odds ratio (FD vs controls)	Pooled odds ratio (if possible)	References
Organic diseases					
Erosive oesophagitis	15/90 (16.7%) with erosive oesophagitis 33/320 (10.3%) with erosive oesophagitis Total = 48/410 (11.7%)	24/273 (8.8%) with erosive oesophagitis 20/320 (6.25%) with erosive oesophagitis Total = 44/593 (7.4%)	OR 2.08 (1.04-4.04), p = 0.049 for erosive oesophagitis OR 1.72 (0.96-3.07), p = 0.08 for erosive oesophagitis	Pooled OR = 1.65 (1.07-2.51), p = 0.026 for erosive oesophagitis	(Jung et al., 2016) (Lasa et al., 2017)
Hiatus hernia	375/5,950 (6.3%) with hiatus hernia	5,884/294,202 (2.0%) with hiatus hernia	OR 3.0 (1.8-2.3) for hiatus hernia		(Garcia-Etxebarria et al., 2022)
Oesophageal cancer	~2/1,669 (0.1%) with oesophageal cancer	~0/83,450 (0.0%) with oesophageal cancer	OR ∞ (23.13-infinity), p = 0.0004 for oesophageal cancer		(Brook et al., 2012)
Erosive gastritis	105/320 (32.8%) with erosive gastritis	57/320 (17.8%) with erosive gastritis	OR 2.25 (1.55-19.04), p < 0.001 for erosive gastritis		(Lasa et al., 2017)
Peptic ulcer disease	~70/1,669 (4.2%) with gastro-duodenal ulcer 16/320 (5.0%) with	~250/83,450 (0.3%) with gastro-duodenal ulcer 9/320 (2.81%) with	OR 14.57 (11.17-18.98), p < 0.0001 for gastro-duodenal ulcer OR 1.81 (0.79-4.17),	Pooled OR = 14.57 (11.37-18.70), p < 0.0001 for peptic ulcers	(Brook et al., 2012) (Lasa et al., 2017)

Systematic review of comorbidities

	gastric ulcers Total = 86/1,989 (4.3%)	gastric ulcers Total = 259/83,770 (0.3%)	p = 0.2 for gastric ulcers		
Gastritis and duodenitis	~399/1,669 (23.9%) with gastritis/duodenitis	~1,419/83,450 (1.7%) with gastritis/duodenitis	OR 18.16 (16.00-20.55), p < 0.0001 for gastritis/duodenitis		(Brook et al., 2012)
Atrophic gastritis	282/694 (40.6%) with atrophic gastritis 56/176 (31.8%) with atrophic gastritis Total = 338/870 (38.9%)	1,128/2,705 (41.7%) with atrophic gastritis 571/1,538 (37.1%) with atrophic gastritis Total = 1,699/4,243 (40.0%)	OR 0.96 (0.81-1.14), p = 0.63 for atrophic gastritis OR 0.79 (0.56-1.10), p = 0.19 for atrophic gastritis	Pooled OR = 0.95 (0.82-1.11), p = 0.52 for atrophic gastritis	(Kim et al., 2014) (Kim et al., 2018a)
Stomach cancer	~2/1,669 (0.1%) with stomach cancer	~0/83,450 (0.0%) with stomach cancer	OR ∞ (23.13-infinity), p < 0.0001 for stomach cancer		(Brook et al., 2012)
Non-infectious gastro-enteritis	~105/1,669 (6.3%) with non-infectious gastro-enteritis	~1,419/83,450 (1.7%) with non-infectious gastro-enteritis	OR 3.88 (3.15-4.74), p < 0.0001 for non-infectious gastro-enteritis		(Brook et al., 2012)
Diabetes mellitus	69/586 (11.8%) with diabetes mellitus	293/2,879 (10.2%) with diabetes mellitus	OR 1.18 (0.89-1.55), p = 0.27 for diabetes mellitus	Pooled OR = 1.38 (1.14-1.68), p = 0.0017 for diabetes mellitus	(Koloski et al., 2019)

Chapter 3

	22/239 (9.2%) with diabetes mellitus	81/1,249 (6.5%) with diabetes mellitus	OR 1.46 (0.88-2.37), p = 0.13 for diabetes mellitus		(Lu et al., 2005)
	58/201 (28.9%) with diabetes mellitus	113/325 (34.9%) with diabetes mellitus	OR 0.76 (0.52-1.12), p = 0.18 for diabetes mellitus		(Park et al., 2021)
	Total = 149/1,026 (14.5%)	Total = 487/4,453 (10.9%)			
H. pylori infection	196/491 (39.9%) with <i>H. pylori</i> infection	379/1,031 (36.8%) with <i>H. pylori</i> infection	OR 1.14 (0.91-1.42), p = 0.24 for <i>H. pylori</i> infection	Pooled OR = 0.73 (0.66- 0.81), p < 0.0001 for <i>H. pylori</i> infection	(Fang et al., 2015)
	12/94 (12.7%) with <i>H. pylori</i> infection	8/52 (15.4%) with <i>H. pylori</i> infection	OR 0.80 (0.31-2.12), p = 0.80 for <i>H. pylori</i> infection		(Futagami et al., 2013a)
	4/25 (16.0%) with <i>H. pylori</i> infection	3/25 (12.0%) with <i>H. pylori</i> infection	OR 1.40 (0.34-6.03), p > 0.99 for <i>H. pylori</i> infection		(Jonsson et al., 1995)
	56/90 (62.2%) with <i>H. pylori</i> infection	149/273 (54.6%) with <i>H. pylori</i> infection	OR 1.37 (0.85-2.23), p = 0.22 for <i>H. pylori</i> infection		(Jung et al., 2016)
	422/694 (60.8%) with <i>H. pylori</i> infection	1,632/2,705 (60.3%) with <i>H. pylori</i> infection	OR 1.02 (0.86-1.21), p = 0.83 for <i>H. pylori</i> infection		(Kim et al., 2014)
	71/176 (40.3%) with <i>H. pylori</i> infection	803/1,538 (52.2%) with <i>H. pylori</i> infection	OR 0.62 (0.45-0.85), p = 0.0032 for <i>H. pylori</i> infection		(Kim et al., 2018a)

Systematic review of comorbidities

	6/36 (16.7%) with <i>H. pylori</i> infection	9/77 (11.7%) with <i>H. pylori</i> infection	OR 1.51 (0.47-4.64), p = 0.55 for <i>H. pylori</i> infection		(Locke et al., 2000)
	74/296 (25.0%) with current <i>H. pylori</i> infection	83/334 (24.9%) with current <i>H. pylori</i> infection	OR 1.01 (0.70-1.44), p > 0.99 for current <i>H. pylori</i> infection		(Nam et al., 2021)
	8/16 (50.0%) with <i>H. pylori</i> infection	8/19 (42.1%) with <i>H. pylori</i> infection	OR 1.38 (0.34-4.84), p = 0.74 for <i>H. pylori</i> infection		(Takamori et al., 2007)
	13/51 (25.5%) with <i>H. pylori</i> infection	14/48 (29.2%) with <i>H. pylori</i> infection	OR 0.83 (0.36-1.97), p = 0.82 for <i>H. pylori</i> infection		(Talley et al., 2007)
	64/114 (56.1%) with <i>H. pylori</i> infection (current or past) Total = 926/2,083 (44.5%)	562/877 (64.1%) with <i>H. pylori</i> infection (current or past) Total = 3,650/6,979 (52.3%)	OR 0.72 (0.48-1.07), p = 0.10 for <i>H. pylori</i> infection		(Zagari et al., 2010)
History of <i>H. pylori</i> eradication	112/296 (37.8%) with a history of <i>H. pylori</i> eradication	85/334 (25.4%) with a history of <i>H. pylori</i> eradication	OR 1.78 (1.27-2.50), p = 0.001 for history of <i>H. pylori</i> eradication		(Nam et al., 2021)
Endocrine autoimmune disorders	33/3,477 (1.0%) with endocrine autoimmune disorders	85/10,926 (0.8%) with endocrine autoimmune disorders	OR 1.22 (0.82-1.81), p = 0.33 for endocrine autoimmune disorders		(Ford et al., 2014)

Chapter 3

Rheumatological disorders	118/3,477 (3.4%) with rheumatological autoimmune disorders	267/10,926 (2.4%) with rheumatological autoimmune disorders	OR 1.40 (1.13-1.75), p = 0.0031 for rheumatological disorders		(Ford et al., 2014)
Any autoimmune disorder	168/3,477 (4.8%) with any autoimmune disorder	392/10,926 (3.6%) with any autoimmune disorder	OR 1.36 (1.13-1.64), p = 0.0012 for any autoimmune disorder		(Ford et al., 2014)
Atopy	1,454/3,477 (41.8%) with atopy	3,575/10,926 (32.7%) with atopy	OR 1.48 (1.37-1.60), p < 0.0001 for atopy		(Jones et al., 2014)
Eczema	955/3,477 (27.5%) with eczema	2,334/10,926 (21.4%) with eczema	OR 1.39 (1.28-1.52), p < 0.0001 for eczema		(Jones et al., 2014)
Hay fever/rhinitis	270/3,477 (7.8%) with hay fever/rhinitis	541/10,926 (5.0%) with hay fever/rhinitis	OR 1.62 (1.39-1.88), p < 0.0001 for hay fever/rhinitis		(Jones et al., 2014)
Allergic conjunctivitis	108/3,477 (3.1%) with allergic conjunctivitis	212/10,926 (1.9%) with allergic conjunctivitis	OR 1.62 (1.28-2.05), p < 0.0001 for allergic conjunctivitis		(Jones et al., 2014)
Asthma	982/5,950 (16.5%) with asthma 517/3,477 (14.9%) with asthma 129/586 (22.0%) with asthma	44,130/294,202 (15.0%) with asthma 1,202/10,926 (11.0%) with asthma 425/2,879 (14.8%) with asthma	OR 1.2 (1.1–1.3) for asthma OR 1.41 (1.27-1.58), p < 0.0001 for asthma OR 1.63 (1.31-2.03), p < 0.0001 for asthma	Pooled OR = 1.11 (1.05-1.18), p = 0.0001 for asthma	(Garcia-Etxebarria et al., 2022) (Jones et al., 2014) (Koloski et al., 2019)

Systematic review of comorbidities

	Total = 1,628/ 10,013 (16.3%)	Total = 45,757/ 308,007 (14.9%)			
Systemic sclerosis	2/586 (0.3%) with systemic sclerosis	7/2,879 (0.2%) with systemic sclerosis	OR 1.41 (0.29-6.23), p = 0.65 for systemic sclerosis		(Koloski et al., 2019)
Psoriasis	33/586 (5.6%) with psoriasis	117/2,879 (4.1%) with psoriasis	OR 1.41 (0.95-2.08), p = 0.095 for psoriasis		(Koloski et al., 2019)
Rheumatoid arthritis	50/586 (8.5%) with rheumatoid arthritis	177/2,879 (6.1%) with rheumatoid arthritis	OR 1.42 (1.02-1.97), p = 0.043 for rheumatoid arthritis		(Koloski et al., 2019)
Coeliac disease	4/320 (1.3%) with coeliac disease	2/320 (0.6%) with coeliac disease	OR 2.01 (0.47-10.63), p = 0.69 for coeliac disease		(Lasa et al., 2017)
Food allergy	64/586 (10.9%) with food allergy	153/2,879 (5.3%) with food allergy	OR 2.18 (1.60-2.96), p < 0.0001 for food allergy		(Koloski et al., 2019)
Pollen allergy	58/586 (9.9%) with pollen allergy	202/2,879 (7.0%) with pollen allergy	OR 1.46 (1.07-1.98), p = 0.020 for pollen allergy		(Koloski et al., 2019)
Animal allergy	27/586 (4.6%) with animal allergy	103/2,879 (3.6%) with animal allergy	OR 1.30 (0.84-2.01), p = 0.23 for animal allergy		(Koloski et al., 2019)
Small intestinal bacterial overgrowth (SIBO)	75/156 (48.1%) with SIBO 8/59 (13.6%) with SIBO	2/40 (5.0%) with SIBO 6/58 (10.3%) with SIBO	OR 17.59 (4.75-75.64), p < 0.0001 for SIBO OR 1.36 (0.41-4.35),	Pooled OR = 6.22 (3.10-12.20), p < 0.0001 for SIBO	(Chojnacki et al., 2020) (Chuah et al., 2022)

Chapter 3

	13/23 (56.5%) with SIBO 44/227 (19.4%) with SIBO Total = 140/465 (30.1%)	0/11 (0.0%) with SIBO 1/30 (3.3%) with SIBO Total = 9/139 (6.5%)	p = 0.78 for SIBO OR ∞ (2.88- infinity), p = 0.0018 for SIBO OR 6.97 (1.25-73.23), p = 0.037 for SIBO		(Costa et al., 2012) (Tziatzios et al., 2021)
Diverticular disease	~78/1,669 (4.7%) with diverticulosis/ -itis 131/5,950 (2.2%) with diverticular disease/ diverticulitis Total = 209/7,619 (2.7%)	~918/83,450 (1.1%) with diverticulosis/ -itis 4,119/ 294,202 (1.4%) with diverticular disease/ diverticulitis Total = 5,037/377,6 52 (1.3%)	OR 4.41 (3.46- 5.56), p < 0.0001 with diverticulosis/ -itis OR 1.4 (1.1- 1.7) for diverticular disease/ diverticulitis	Pooled OR = 2.09 (1.81- 2.40), p < 0.0001 for diverticular disease	(Brook et al., 2012) (Garcia- Etxebarria et al., 2022)
Infectious gastroenteritis	~27/1,669 (1.6%) with intestinal infection	~501/83,450 (0.6%) with intestinal infection	OR 2.72 (1.85-3.99), p < 0.0001 for intestinal infection		(Brook et al., 2012)
Enteritis/ ulcerative colitis	~33/1,669 (2.0%) with enteritis/ ulcerative colitis	~334/83,450 (0.4%) with enteritis/ ulcerative colitis	OR 5.02 (3.52-7.14), p < 0.0001 for enteritis/ ulcerative colitis		(Brook et al., 2012)
Appendicitis	~8/1,669 (0.5%) with appendicitis	~167/83,450 (0.2%) with appendicitis	OR 2.40 (1.15-4.69), p = 0.023 for appendicitis		(Brook et al., 2012)

Systematic review of comorbidities

Intestinal obstruction without hernia	~22/1,669 (1.3%) with intestinal obstruction	~167/83,450 (0.2%) with intestinal obstruction	OR 6.66 (4.31-10.33), p < 0.0001 for intestinal obstruction		(Brook et al., 2012)
Abdominal hernia	~118/1,669 (7.1%) with abdominal hernia	~835/83,450 (1.0%) with abdominal hernia	OR 7.53 (6.16-9.17), p < 0.0001 for abdominal hernia		(Brook et al., 2012)
Gastro-intestinal (GI) haemorrhage	~139/1,669 (8.3%) with GI bleeding	~1,586/83,450 (1.9%) with GI bleeding	OR 4.69 (3.91-5.61), p < 0.0001 for GI bleeding		(Brook et al., 2012)
Haemorrhoids	~97/1,669 (5.8%) with haemorrhoids	~1,252/83,450 (1.5%) with haemorrhoids	OR 4.05 (3.28-5.00), p < 0.0001 for haemorrhoids		(Brook et al., 2012)
Cancer of colon	~5/1,669 (0.3%) with colon cancer	~83/83,450 (0.1%) with colon cancer	OR 3.02 (1.31-7.11), p = 0.030 for colon cancer		(Brook et al., 2012)
Cancer of rectum and anus	~3/1,669 (0.2%) with cancer of rectum and anus	~83/83,450 (0.1%) with cancer of rectum and anus	OR 1.81 (0.59-5.41), p = 0.24 for cancer of rectum and anus		(Brook et al., 2012)
Peritonitis	~8/1,669 (0.5%) with peritonitis/intestinal abscess	~0/83,450 (0.0%) with peritonitis/intestinal abscess	OR ∞ (112.2-infinity), p < 0.0001 for peritonitis/intestinal abscess		(Brook et al., 2012)
Cancer of peritoneum	~2/1,669 (0.1%) with peritoneal cancer	~0/83,450 (0.0%) with peritoneal cancer	OR ∞ (23.13-infinity), p = 0.0004 for peritoneal cancer		(Brook et al., 2012)

Chapter 3

Hepatitis	~28/1,669 (1.7%) with hepatitis	~501/83,450 (0.6%) with hepatitis	OR 2.83 (1.91-4.10), p < 0.0001 for hepatitis		(Brook et al., 2012)
Biliary tract disease	~112/1,669 (6.7%) with biliary tract disease	~668/83,450 (0.8%) with biliary tract disease	OR 8.91 (7.24-10.96), p < 0.0001 for biliary tract disease		(Brook et al., 2012)
Gallstones	262/5,950 (4.4%) with gallstones 22/239 (9.2%) with gallstones Total = 284/6,189 (4.6%)	5,884/ 294,202 (2.0%) with gallstones 86/1,249 (6.9%) with gallstones Total = 5,970/ 295,451 (2.0%)	OR 1.9 (1.7– 2.2) for gallstones OR 1.37 (0.82-2.21), p = 0.22 for gallstones	Pooled OR = 2.33 (2.07- 2.63), p < 0.0001 for gallstones	(Garcia-Etxebarria et al., 2022) (Lu et al., 2005)
Cancer of the liver/biliary tract	~0/1,669 (0.0%) with cancer of the liver/ hepatic bile duct	~17/83,450 (0.02%) with cancer of the liver/ hepatic bile duct	OR 0.00 (0.00-10.41), p > 0.99 for cancer of the liver/ hepatic bile duct		(Brook et al., 2012)
Pancreatic disease	~22/1,669 (1.3%) with pancreatic disease	~167/83,450 (0.2%) with pancreatic disease	OR 6.66 (4.31- 10.33), p < 0.0001 for pancreatic disease		(Brook et al., 2012)
Impaired pancreatic function	6/22 (27.3%) with impaired pancreatic function	0/17 (0.0%) with impaired pancreatic function	OR ∞ (1.65- infinity), p = 0.027 for impaired pancreatic function		(Smith et al., 1991)
Cancer of the pancreas	~3/1,669 (0.2%) with cancer of the pancreas	~0/83,450 (0.0%) with cancer of the pancreas	OR ∞ (43.35- infinity), p < 0.0001 for cancer of the pancreas		(Brook et al., 2012)

Systematic review of comorbidities

Chronic obstructive pulmonary disease (COPD)	137/5,950 (2.3%) with emphysema/ chronic bronchitis	4,707/ 294,202 (1.6%) with emphysema/ chronic bronchitis	OR 1.4 (1.2–1.7) for COPD		(Garcia-Etxebarria et al., 2022)
Acute bronchitis	~147/1,669 (8.8%) with acute bronchitis	~4,423/ 83,450 (5.3%) with acute bronchitis	OR 1.73 (1.45-2.05), $p < 0.0001$ for acute bronchitis		(Brook et al., 2012)
Other upper respiratory infections	~532/1,669 (31.9%) with other upper respiratory infections	~16,273/ 83,450 (19.5%) with other upper respiratory infections	OR 1.93 (1.74-2.14), $p < 0.0001$ for other upper respiratory infections		(Brook et al., 2012)
Hyperlipidaemia	~354/1,669 (21.2%) with hyperlipidaemia	~10,097/ 83,450 (12.1%) with hyperlipidaemia	OR 1.96 (1.74-2.20), $p < 0.0001$ for hyperlipidaemia		(Brook et al., 2012)
Urinary tract infections	~165/1,669 (9.9%) with urinary tract infections	~4,423/ 83,450 (5.3%) with urinary tract infections	OR 1.96 (1.66-2.31), $p < 0.0001$ for urinary tract infections		(Brook et al., 2012)
Essential hypertension	~297/1,669 (17.8%) with hypertension 51/239 (21.3%) with hypertension 75/201 (37.3%) with hypertension Total = 423/2,109 (20.1%)	~10,348/ 83,450 (12.4%) with hypertension 301/1,249 (24.1%) with hypertension 139/325 (42.8%) with hypertension Total = 10,788/85,024 (12.7%)	OR 1.53 (1.35-1.74), $p < 0.0001$ for hypertension OR 0.85 (0.61-1.19), $p = 0.41$ for hypertension OR 0.80 (0.55-1.15), $p = 0.24$ for hypertension	Pooled OR = 1.73 (1.55-1.92), $p < 0.0001$ for essential hypertension	(Brook et al., 2012) (Lu et al., 2005) (Park et al., 2021)

Non-specific chest pain	~334/1,669 (20.0%) with non-specific chest pain	~5,758/83,450 (6.9%) with non-specific chest pain	OR 3.38 (2.99-3.82), $p < 0.0001$ for non-specific chest pain		(Brook et al., 2012)
Angina	393/5,950 (6.6%) with angina	10,885/294,202 (3.7%) with angina	OR 1.9 (1.7–2.1) for angina		(Garcia-Etxebarria et al., 2022)
Myocardial infarction	232/5,950 (3.9%) with myocardial infarction	8,238/294,202 (2.8%) with myocardial infarction	OR 1.6 (1.3–1.8) for myocardial infarction		(Garcia-Etxebarria et al., 2022)
Osteoporosis	220/5,950 (3.7%) with osteoporosis	5,884/294,202 (2.0%) with osteoporosis	OR 1.5 (1.3–1.7) for osteoporosis		(Garcia-Etxebarria et al., 2022)
Osteoarthritis	881/5,950 (14.8%) with osteoarthritis	32,656/294,202 (11.1%) with osteoarthritis	OR 1.2 (1.1–1.3) for osteoarthritis		(Garcia-Etxebarria et al., 2022)
Joint hypermobility syndrome	43/101 (42.6%) with joint hypermobility syndrome	84/305 (27.5%) with joint hypermobility syndrome	OR 1.95 (1.23–3.07), $p = 0.0063$ for joint hypermobility syndrome		(Fikree et al., 2015)
Inter-vertebral disc disorders	~369/1,669 (22.1%) with inter-vertebral disc disorders	~10,598/83,450 (12.7%) with inter-vertebral disc disorders	OR 1.95 (1.74-2.19), $p < 0.0001$ for inter-vertebral disc disorders		(Brook et al., 2012)
Disk hernia	~173/5,950 (2.9%) with prolapsed disk/slipped disk	6,767/294,202 (2.3%) with prolapsed disk/slipped disk	OR 1.3 (1.1–1.6) for disk hernia		(Garcia-Etxebarria et al., 2022)

Systematic review of comorbidities

Spine arthritis/ spondylitis	107/5,950 (1.8%) with spine arthritis/ spondylitis	3,236/ 294,202 (1.1%) with spine arthritis/ spondylitis	OR 1.5 (1.2–1.9) for spine arthritis/ spondylitis		(Garcia-Etxebarria et al., 2022)
Sprains and strains	~199/1,669 (11.9%) with sprains and strains	~6,759/ 83,450 (8.1%) with sprains and strains	OR 1.54 (1.32-1.78), p < 0.0001 for sprains and strains		(Brook et al., 2012)
Ovarian cysts	107/5,950 (1.8%) with ovarian cysts	3,236/ 294,202 (1.1%) with ovarian cysts	OR 1.4 (1.1–1.7) for ovarian cysts		(Garcia-Etxebarria et al., 2022)
Enlarged prostate	125/5,950 (2.1%) with enlarged prostate	5,884/ 294,202 (2.0%) with enlarged prostate	OR 1.4 (1.1–1.6) for enlarged prostate		(Garcia-Etxebarria et al., 2022)
Pulmonary embolism ± deep vein thrombosis (DVT)	89/5,950 (1.5%) with pulmonary embolism ± DVT	2,942/ 294,202 (1.0%) with pulmonary embolism ± DVT	OR 1.4 (1.1–1.7) for pulmonary embolism ± DVT		(Garcia-Etxebarria et al., 2022)
Other DGBI					
Gastro-oesophageal reflux disease (GORD)	970/5,950 (16.3%) with GORD 18/40 (45.0%) with GORD symptoms 178/384 (46.4%) with GORD 147/296 (49.7%) with GORD	12,651/ 294,202 (4.3%) with GORD 7/78 (9.0%) with GORD symptoms 178/4,616 (3.86%) with GORD 17/334 (5.1%) with GORD	OR 4.3 (3.9–4.6) for GORD OR 8.30 (2.93-20.58), p < 0.0001 for GORD symptoms OR 21.54 (16.75-27.56), p < 0.0001 for GORD OR 18.40 (10.65-31.61), p < 0.0001 for	Pooled OR = 8.24 (7.89-8.61), p < 0.0001 for reflux disease	(Garcia-Etxebarria et al., 2022) (Matsuzaki et al., 2018) (Min et al., 2014) (Nam et al., 2021)

Chapter 3

	symptoms 110/367 (30.0%) with GORD 103/201 (51.2%) with heartburn 1,651/3,599 (45.9%) with GORD 7/31 (22.6%) with GOR symptoms 97/176 (55.1%) with reflux Total = 3,281/11,044 (29.7%)	symptoms 84/472 (17.8%) with GORD 123/325 (37.8%) with heartburn 3,613/43,491 (8.3%) with GORD ~6/128 (4.7%) with GOR symptoms 122/688 (17.7%) with reflux Total = 16,801/344,334 (4.9%)	GORD symptoms OR 1.98 (1.43-2.73), $p < 0.0001$ for GORD OR 1.73 (1.20-2.45), $p = 0.0028$ for heartburn OR 9.35 (8.69-10.07), $p < 0.0001$ for GORD OR 5.93 (1.93-20.26), $p = 0.0041$ for GOR symptoms OR 5.70 (3.98-8.09), $p < 0.0001$ for reflux		(Olmos et al., 2006) (Park et al., 2021) (Rasmussen et al., 2015) (Talley et al., 1990) (Welén et al., 2008)
Functional heartburn	67/551 (12.2%) with functional heartburn	40/5,380 (0.7%) with functional heartburn	OR 18.48 (12.29-27.64), $p < 0.0001$ for functional heartburn		(Aziz et al., 2018a)
Nausea and vomiting	~169/1,669 (10.1%) 16/384 (4.2%) with vomiting 33/296 (11.1%) with vomiting	~1,252/83,450 (1.5%) 9/4,616 (0.19%) with vomiting 4/334 (1.2%) with vomiting	OR 7.40 (6.25-8.75), $p < 0.0001$ OR 22.26 (9.65-52.02), $p < 0.0001$ for vomiting OR 10.35 (3.80-27.50), $p < 0.0001$ for vomiting	Pooled OR = 7.05 (6.06-8.17), $p < 0.0001$ for nausea/vomiting	(Brook et al., 2012) (Min et al., 2014) (Nam et al., 2021)

	Total = 218/2,349 (9.3%)	Total = 1,265/ 88,400 (1.4%)			
<i>Irritable bowel syndrome (IBS)</i>	174/551 (31.6%) with IBS	167/5,380 (3.1%) with IBS	OR 14.41 (11.32-18.21), p < 0.0001 for IBS	Pooled OR = 6.81 (6.51- 7.12), p < 0.0001 for IBS	(Aziz et al., 2018a)
	20/63 (31.7%) with IBS	16/201 (8.0%) with IBS	OR 5.34 (2.62-11.30), p < 0.0001 for IBS		(Caballero- Plasencia et al., 1999)
	88/151 (58.3%) with IBS	12/58 (20.7%) with IBS	OR 5.35 (2.64-10.64), p < 0.0001 for IBS		(Dibaise et al., 2016a)
	12/429 (2.8%) with IBS	375/3,956 (9.5%) with IBS	OR 0.27 (0.15-0.49), p < 0.0001 for IBS		(Dong et al., 2013)
	144/491 (29.3%) with IBS	32/1,031 (3.1%) with IBS	OR 12.96 (8.69-19.36), p < 0.0001 for IBS		(Fang et al., 2015)
	333/5,950 (5.6%) with IBS	7,943/ 294,202 (2.7%) with IBS	OR 2.0 (1.8– 2.3) for IBS		(Garcia- Etxebarria et al., 2022)
	27/90 (30.0%) with IBS	40/273 (14.7%) with IBS	OR 2.50 (1.43-4.40), p = 0.0017 for IBS		(Jung et al., 2016)
	117/438 (26.7%) with IBS	611/4,892 (12.5%) with IBS	OR 2.55 (2.04-3.21), p < 0.0001 for IBS		(Matsuzaki et al., 2012)
	46/202 (22.8%) with IBS	10/257 (3.9%) with IBS	OR 7.28 (3.55-14.76), p < 0.0001 for IBS		(Matsuzaki et al., 2018)
	~10/40 (25.0%) with IBS	~4/78 (5.1%) with IBS	OR 6.17 (1.81-18.65), p = 0.0047 for IBS		(Matsuzaki et al., 2018)

Chapter 3

	91/247 (36.8%) with IBS	4/743 (0.5%) with IBS	OR 107.8 (41.16- 277.9), $p < 0.0001$ for IBS		(Minocha et al., 2006)
	205/440 (46.6%) with IBS	652/4,717 (13.8%) with IBS	OR 5.44 (4.44-6.69), $p < 0.0001$ for IBS		(Oshima et al., 2021)
	105/249 (42.2%) with IBS	282/2,715 (10.4%) with IBS	OR 6.29 (4.75-8.33), $p < 0.0001$ for IBS		(Perveen et al., 2014)
	5/39 (12.8%) with IBS	30/94 (31.9%) with IBS	OR 0.31 (0.12-0.86), $p = 0.030$ for IBS		(Pittock et al., 2011)
	1,380/3,599 (38.3%) with IBS	3,531/ 43,491 (8.1%) with IBS	OR 7.04 (6.53-7.59), $p < 0.0001$ for IBS		(Rasmussen et al., 2015)
	8/31 (25.8%) with IBS	9/128 (7.0%) with IBS	OR 4.60 (1.53-12.96), $p = 0.006$ for IBS		(Talley et al., 1990)
	34/176 (19.3%) with IBS	59/688 (8.6%) with IBS	OR 2.55 (1.60-4.01), $p = 0.0001$ for IBS		(Welén et al., 2008)
	19/114 (16.7%) with IBS	49/877 (5.6%) with IBS	OR 3.38 (1.91-5.85), $p < 0.0001$ for IBS		(Zagari et al., 2010)
	Total = 2,818/ 13,300 (21.2%)	Total = 13,826/ 363,781 (3.8%)			
Chronic diarrhoea	7/31 (22.6%) with chronic diarrhoea	19/128 (14.8%) with chronic diarrhoea	OR 1.67 (0.65-4.56), $p = 0.29$ for chronic diarrhoea		(Talley et al., 1990)

Systematic review of comorbidities

Chronic constipation	9/31 (29.0%) with chronic constipation	14/128 (10.9%) with chronic constipation	OR 3.33 (1.35-8.38), p = 0.020 for chronic constipation		(Talley et al., 1990)
Prolonged oro-caecal transit time	10/21 (47.6%) with prolonged oro-caecal transit time	15/24 (62.5%) with prolonged oro-caecal transit time	OR 0.54 (0.17-1.94), p = 0.38 for prolonged oro-caecal transit time		(Lorena et al., 2002a)
Excessive duodeno-gastric reflux	27/61 (44.3%) with excessive duodeno-gastric reflux	2/41 (4.9%) with excessive duodeno-gastric reflux	OR 15.49 (3.56-68.55), p < 0.0001 for excessive duodeno-gastric reflux		(Fein et al., 2002)
Non-GI functional somatic disorders					
Headache/migraine	~177/1,669 (10.6%) with headache, including migraine 327/5,950 (5.5%) with migraine 36/240 (15.0%) with migraine Total = 540/7,859 (6.9%)	~4,673/83,450 (5.6%) with headache, including migraine 12,356/294,202 (4.2%) with migraine 35/310 (11.3%) with migraine Total = 17,064/377,962 (4.5%)	OR 2.00 (1.70-2.34), p < 0.0001 for headache, including migraine OR 1.3 (1.1-1.4) for migraine OR 1.39 (0.85-2.27), p = 0.20 for migraine	Pooled OR = 1.56 (1.43-1.71), p < 0.0001 for headache	(Brook et al., 2012) (Garcia-Etxebarria et al., 2022) (Meucci et al., 2005)
Overactive bladder	90/438 (20.5%) with overactive bladder	407/4,892 (8.3%) with overactive bladder	OR 2.85 (2.21-3.67), p < 0.0001 for overactive bladder		(Matsuzaki et al., 2012)

Chapter 3

Chronic fatigue	~212/1,669 (12.7%) with malaise and fatigue	~4,673/83,450 (5.6%) with malaise and fatigue	OR 2.45 (2.11-2.84), $p < 0.0001$ for fatigue		(Brook et al., 2012)
Low back pain	196/5,950 (3.3%) with back problems	6,767/294,202 (2.3%) with back problems	OR 1.5 (1.3–1.7) for back problems		(Garcia-Etxebarria et al., 2022)
Sexual dysfunction	112/242 (46.3%) with sexual dysfunction	31/193 (16.1%) with sexual dysfunction	OR 4.50 (2.83-7.02), $p < 0.0001$ for sexual dysfunction		(Fass et al., 1998)
Psychological attributes and psychiatric conditions					
Psychiatric disorders	34/100 (34.0%) with psychiatric diagnoses 9/90 (10.0%) with a history of neuro-psychiatric disease 15/18 (83.3%) with current psychiatric disorders Total = 58/208 (27.9%)	1/100 (1%) with psychiatric diagnosis 14/273 (5.1%) with a history of neuro-psychiatric disease 16/49 (32.7%) with current psychiatric disorders Total = 31/422 (7.3%)	OR 51.0 (9.33-526.8), $p < 0.0001$ for psychiatric diagnoses OR 2.06 (0.83-4.89), $p = 0.13$ for neuro-psychiatric disease OR 10.31 (2.66-36.00), $p = 0.0003$ for current psychiatric disorders	Pooled OR = 4.88 (3.02-7.79), $p < 0.0001$ for psychiatric disorders	(Haug et al., 1994) (Jung et al., 2016) (Malt et al., 2000)
Anxiety disorder	9/18 (50.0%) with lifetime anxiety disorder	16/49 (32.7%) with lifetime anxiety disorder	OR 2.06 (0.66-6.55), $p = 0.26$ for lifetime anxiety disorder		(Malt et al., 2000)

Anxiety (trait)	/	/	OR 2.56 (1.06-6.19) for major anxiety OR 1.26 (0.67-2.31), p = 0.54 for anxiety OR 4.70 (3.74-5.91), p < 0.0001 for anxiety OR 1.6 (1.4-1.9) for anxiety/panic attacks OR 4.54 (1.88-10.45), p = 0.0006 for anxiety OR 2.21 (1.90-2.57), p < 0.0001 for anxiety OR 1.14 (0.28-5.00), p > 0.99 for general anxiety OR 5.13 (2.13-11.43), p = 0.0001 for anxiety OR 5.95 (4.01-8.70), p < 0.0001 for anxiety OR 2.96 (1.48-5.92), p = 0.0029 for trait anxiety OR 5.56 (1.53-20.00), p = 0.014 for anxiety	Pooled OR = 5.71 (5.35-6.09), p < 0.0001 for anxiety	
	71/151 (47.0%) with anxiety	24/58 (41.4%) with anxiety			(Aro et al., 2009)
	332/491 (64.8%) with anxiety	304/1,031 (29.5%) with anxiety			(Dibaise et al., 2016a)
	~179/5,950 (3.0%) with anxiety/panic attacks	5,590/294,202 (1.9%) with anxiety/panic attacks			(Fang et al., 2015)
	27/62 (43.5%) with anxiety	9/62 (14.5%) with anxiety			(Garcia-Etxebarria et al., 2022)
	293/3,477 (8.4%) with anxiety	437/10,926 (4.0%) with anxiety			(Hartono et al., 2012)
	4/25 (16.0%) with general anxiety	3/21 (14.3%) with general anxiety			(Jones et al., 2014)
	22/40 (55.0%) with anxiety	15/78 (19.2%) with anxiety			(Jonsson et al., 1995)
	137/201 (68.2%) with anxiety	86/325 (26.5%) with anxiety			(Matsuzaki et al., 2018)
	60/96 (62.5%) with trait anxiety	18/50 (36.0%) with trait anxiety			(Park et al., 2021)
	35/38 (92.1%) with significant anxiety	21/31 (67.7%) with significant anxiety			(Tominaga et al., 2007)
					(Vishnar et al., 2000)

Chapter 3

	26/176 (14.8%) with anxiety Total = 1,186/ 10,707 (11.1%)	63/688 (9.2%) with anxiety Total = 6,570/ 307,472 (2.1%)	OR 1.72 (1.064-2.83), p = 0.037 for anxiety		(Welén et al., 2008)
Anxiety (state)	71/96 (74.0%) with state anxiety	25/50 (50.0%) with state anxiety	OR 2.84 (1.37-5.64), p = 0.0056 for state anxiety		(Tominaga et al., 2007)
Panic disorder	2/25 (8.0%) with panic disorder 0/18 (0.0%) with lifetime panic disorder Total = 2/43 (4.7%)	0/21 (0.0%) with panic disorder 1/49 (2.0%) lifetime panic disorder Total = 1/70 (1.4%)	OR ∞ (0.39- infinity), p = 0.49 for panic disorder OR 0.00 (0.00-24.50), p > 0.99 for lifetime panic disorder	Pooled OR = 3.37 (0.38- 49.37), p = 0.56 for panic disorders	(Jonsson et al., 1995) (Malt et al., 2000)
Agoraphobia	4/18 (22.2%) with lifetime agoraphobia	0/49 (0.0%) lifetime agoraphobia	OR ∞ (2.89- infinity), p = 0.0040 for lifetime agoraphobia		(Malt et al., 2000)
Any mood (affective) disorder	~125/1,669 (7.5%) with any affective disorder 76/128 (59.38%) with any mood disorder	~2,670/ 83,450 (3.2%) with any affective disorder 145/631 (22.98%) with any mood disorder	OR 2.45 (2.04-2.95), p < 0.0001 for any affective disorder OR 4.90 (3.26-7.35), p < 0.0001 for any mood disorder	Pooled OR = 3.89 (3.35- 4.50), p < 0.0001 for mood disorders	(Brook et al., 2012) (Huang et al., 2020)

Systematic review of comorbidities

	15/18 (83.3%) with lifetime mood disorder Total = 216/1,815 (11.9%)	12/49 (24.5%) with lifetime mood disorder Total = 2,827/ 84,130 (3.4%)	OR 15.42 (3.78-54.14), p < 0.0001 for lifetime mood disorder		(Malt et al., 2000)
Depression	65/151 (43.0%) with depression 266/491 (54.2%) with depression 58/60 (96.7%) with depression 524/5,950 (8.8%) with depression 14/62 (22.6%) with depression 579/3,477 (16.7%) with depression 1/25 (4.0%) with depression 12/40 (30.0%) with depression	24/58 (41.4%) with depression 272/1,031 (26.4%) with depression 6/60 (10.0%) with depression 22,654/ 294,202 (7.7%) with depression 4/62 (6.5%) with depression 1,151/ 10,926 (10.5%) with depression 0/21 (0.0%) with depression 14/78 (17.9%) with depression	OR 1.07 (0.57-1.97), p = 0.88 for depression OR 3.30 (2.64- 4.14), p < 0.0001 for depression OR 261.0 (50.71- 1,158), p < 0.0001 for depression OR 1.2 (1.1- 1.3) for depression OR 4.23 (1.30-12.29), p = 0.020 for depression OR 1.70 (1.52- 1.89), p < 0.0001 for depression OR ∞ (0.093- infinity), p > 0.99 for depression OR 1.96 (0.83-4.51), p = 0.16 for depression	Pooled OR = 2.20 (2.08- 2.32), p < 0.0001 for depression	(Dibaise et al., 2016a) (Fang et al., 2015) (Filipović et al., 2013) (Garcia- Etxebarria et al., 2022) (Hartono et al., 2012) (Jones et al., 2014) (Jonsson et al., 1995) (Matsuzaki et al., 2018)

	136/201 (67.8%) with depression 13/76 (17.1%) with clinical depression 27/96 (28.1%) with depression 12/176 (6.8%) with depression Total = 1,707/ 10,805 (15.8%)	56/325 (17.2%) with depression 10/76 (13.2%) with clinical depression ~6/50 (12.0%) with depression 18/688 (2.6%) with depression Total = 24,215/ 307,577 (7.9%)	OR 10.05 (6.57-15.24), p < 0.0001 for depression OR 1.36 (0.57-3.39), p = 0.65 for depression OR 2.87 (1.15-7.26), p = 0.036 for depression OR 2.72 (1.30-5.55), p = 0.011 for depression		(Park et al., 2021) (Talley et al., 1986) (Tominaga et al., 2007) (Welén et al., 2008)
Anxiety/ depression	168/384 (43.8%) with moderate anxiety/ depression 122/201 (60.7%) with anxiety + depression Total = 290/ 585 (49.6%)	869/4,616 (18.8%) with moderate anxiety/ depression 47/325 (14.5%) with anxiety + depression Total = 916/ 4,941 (18.5%)	OR 4.25 (3.43- 5.25), p < 0.0001 for moderate- severe anxiety/ depression OR 9.13 (6.02-13.71), p < 0.0001 for anxiety/ depression	Pooled OR = 4.32 (3.62- 5.15), p < 0.0001 for anxiety/ depression	(Min et al., 2014) (Park et al., 2021)
Sleep disturbance	330/491 (67.2%) with sleep disturbance 140/200 (70.0%) with sleep dysfunction	412/1,031 (40.0%) with sleep disturbance 113/205 (55.1%) with sleep dysfunction	OR 3.08 (2.45-3.85), p < 0.0001 for sleep disturbance OR 1.90 (1.26-2.83), p = 0.0021 for sleep dysfunction	Pooled OR = 2.91 (2.57- 3.30), p < 0.0001 for sleep disturbance	(Fang et al., 2015) (Fass et al., 2000)

Systematic review of comorbidities

	46/94 (48.9%) with sleep disorder	11/57 (19.3%) with sleep disorder	OR 4.01 (1.86-8.54), p = 0.0003 for sleep disorder		(Futagami et al., 2013a)
	85/121 (70.2%) with occasional sleep problems	30/50 (60.0%) with occasional sleep problems	OR 1.57 (0.78-3.07), p = 0.21 for occasional sleep problems		(Lacy et al., 2011)
	95/239 (39.7%) with sleep disturbance	234/1,249 (18.7%) with sleep disturbance	OR 2.86 (2.12-3.83), p < 0.0001 for sleep disturbance		(Lu et al., 2005)
	84/201 (41.8%) with sleep disorders	61/325 (18.8%) with sleep disorders	OR 3.11 (2.08-4.61), p < 0.0001 for sleep disorders		(Park et al., 2021)
	79/176 (44.9%) with sleep problems	249/688 (36.2%) with sleep problems	OR 1.44 (1.02-2.01), p = 0.037 for sleep problems		(Welén et al., 2008)
	Total = 859/1,522 (56.4%)	Total = 1,110/3,605 (30.8%)			
Insomnia	57/128 (44.5%) with insomnia	174/631 (27.58%) with insomnia	OR 2.11 (1.44-3.12), p = 0.0002 for insomnia		(Huang et al., 2020)
Impaired sleep quality	27/29 (93.1%) with poor sleep quality	81/122 (66.4%) with poor sleep quality	OR 6.83 (1.69-30.11), p = 0.0029 for poor sleep quality	Pooled OR = 1.88 (1.38- 2.55), p < 0.0001 for impaired sleep quality	(Lim et al., 2017)
	101/202 (50.0%) with impaired sleep quality	86/257 (33.5%) with impaired sleep quality	OR 1.99 (1.35-2.90), p = 0.0004 for impaired sleep quality		(Matsuzaki et al., 2018)

Chapter 3

	~26/40 (65.0%) with impaired sleep quality Total = 154/271 (56.8%)	21/78 (26.9%) with impaired sleep quality Total = 188/457 (41.1%)	OR 5.04 (2.20-11.80), p = 0.0001 for impaired sleep quality		(Matsuzaki et al., 2018)
Trouble falling asleep	52/121 (43.0%) with trouble falling asleep	14/50 (28.0%) with trouble falling asleep	OR 1.94 (0.98-4.08), p = 0.084 for trouble falling asleep		(Lacy et al., 2011)
Trouble staying asleep	77/121 (63.6%) with trouble staying asleep	18/50 (36.0%) with trouble staying asleep	OR 3.11 (1.54-5.95), p = 0.0012 for trouble staying asleep		(Lacy et al., 2011)
Somatisation	94/151 (62.3%) with somatisation 1/25 (4.0%) with somatisation Total = 95/176 (54.0%)	23/58 (39.7%) with somatisation 0/21 (0.0%) with somatisation Total = 23/79 (29.1%)	OR 2.51 (1.33-4.71) p = 0.0049 for somatisation OR ∞ (0.093- infinity), p > 0.99 for somatisation	Pooled OR = 2.86 (1.63- 4.98), p = 0.0002 for somatisation	(Dibaise et al., 2016a) (Jonsson et al., 1995)
Psychological distress	35/81 (43.2%) with psychological distress /	1/29 (3.45%) with psychological distress /	OR 21.30 (3.50-224.8), p < 0.0001 for psychological distress OR 2.03 (0.74-5.51) for non- serious psychosocial alarm	Pooled OR = 4.48 (3.51- 5.69), p < 0.0001 for psychologic al distress	(Jones and Maganti, 2004) (Koh et al., 2014)

Systematic review of comorbidities

	13/16 (81.3%) with psychosocial symptoms 26/29 (89.7%) with serious psychosocial alarm 78/205 (38.0%) with mental distress Total = 152/331 (45.9%)	73/144 (50.7%) with psychosocial symptoms 69/122 (56.6%) with serious psychosocial alarm 208/1,906 (10.9%) with mental distress Total = 351/2,201 (15.9%)	OR 4.22 (1.15-15.42), p = 0.03 for psychosocial symptoms OR 10.37 (2.60-45.42), p = 0.0002 for serious psychosocial alarm OR 5.01 (3.63-6.90), p < 0.0001 for mental distress		(Lee et al., 2013) (Lim et al., 2017) (Pajala et al., 2005)
Personality (dissociative) disorders	~159/1,669 (9.5%) 2/25 (8.0%) with personality disorder Total = 161/1,694 (9.5%)	~2,921/ 83,450 (3.5%) 1/21 (4.76%) with personality disorder Total = 2,922/ 83,471 (3.5%)	OR 2.90 (2.45-3.43), p < 0.0001 OR 1.74 (0.19-26.32), p > 0.99 for personality disorder	Pooled OR = 2.90 (2.45- 3.42), p < 0.0001 for personality disorders	(Brook et al., 2012) (Jonsson et al., 1995)
Hostility	277/491 (56.4%) with hostility	357/1,031 (34.6%) with hostility	OR 2.44 (1.96-3.05), p < 0.0001 for hostility		(Fang et al., 2015)
Inferiority	125/491 (25.5%) with inferiority	140/1,031 (13.6%) with inferiority	OR 2.17 (1.66- 2.83), p < 0.0001 for inferiority		(Fang et al., 2015)
Chronic stress	69/100 (69.0%) had experienced elements of chronic stress	37/100 (37.0%) had experienced elements of chronic stress	OR 3.79 (2.07-6.62), p < 0.0001 for chronic stress	Pooled OR = 2.66 (2.22- 3.20), p < 0.0001 for chronic stress	(Haug et al., 1995)

Chapter 3

	~426/947 (45.0%) with daily stress Total = 495/1,047 (42.3%)	~240/1,000 (24.0%) with daily stress Total = 277/1,100 (25.2%)	OR 2.59 (2.14-3.14), p < 0.0001 for daily stress		(Miwa, 2012)
Stressful life events	26/47 (55.3%) with any life- threatening event 58/68 (83.8%) with any stressful life event 26/38 (68.4%) with undesirable events (life stress) Total = 110/153 (71.9%)	49/119 (41.2%) with any life- threatening event 57/68 (83.8%) with any stressful life event 24/31 (77.4%) with undesirable events (life stress) Total = 130/218 (59.6%)	OR 1.77 (0.92-3.51), p = 0.12 for any life- threatening event OR 1.12 (0.44-2.96), p > 0.99 for any stressful life event OR 0.63 (0.23-1.77), p = 0.43 for life stress	Pooled OR = 1.73 (1.10- 2.73), p = 0.016 for stressful life events	(Locke et al., 2004b) (Talley and Piper, 1986) (Vishnar et al., 2000)
Any abuse	124/258 (48.1%) with a history of any abuse	39/82 (47.6%) with a history of any abuse	OR 1.02 (0.63-1.67), p > 0.99 for any abuse		(Koloski et al., 2005b)
Childhood abuse	79/258 (30.6%) with a history of childhood abuse 553/1,893 (29.2%) with childhood abuse history	25/79 (31.7%) with a history of childhood abuse 67/472 (14.2%) with childhood abuse history	OR 0.95 (0.55-1.62), p = 0.89 for childhood abuse OR 2.50 (1.89-3.31), p < 0.0001 for childhood abuse history	Pooled OR = 2.08 (1.64- 2.65), p < 0.0001 for childhood abuse history	(Koloski et al., 2005b) (Oshima et al., 2015)

Systematic review of comorbidities

	Total = 632/2,151 (29.4%)	Total = 92/551 (16.7%)			
Adult abuse	97/258 (37.6%) with a history of adulthood abuse	22/83 (25.6%) with a history of adulthood abuse	OR 1.67 (0.96-2.93), p = 0.085 for adult abuse		(Koloski et al., 2005b)
Physical abuse history	162/2073 (7.8%) with physical abuse history	16/485 (3.3%) with physical abuse history	OR 2.49 (1.47-4.25), p = 0.0002 for physical abuse history		(Oshima et al., 2015)
Sexual abuse history	71/2073 (3.4%) with sexual abuse history	2/485 (0.4%) with sexual abuse history	OR 8.57 (2.47-35.78), p < 0.0001 for sexual abuse history		(Oshima et al., 2015)
Psychological abuse history	500/2073 (24.1%) with psychological abuse history	62/485 (12.8%) with psychological abuse history	OR 2.68 (2.04-3.56), p < 0.0001 for psychological abuse history		(Oshima et al., 2015)

The association with IBS in FD patients among the different studies involving a control group is depicted in a Forrest plot in Figure 3.2.

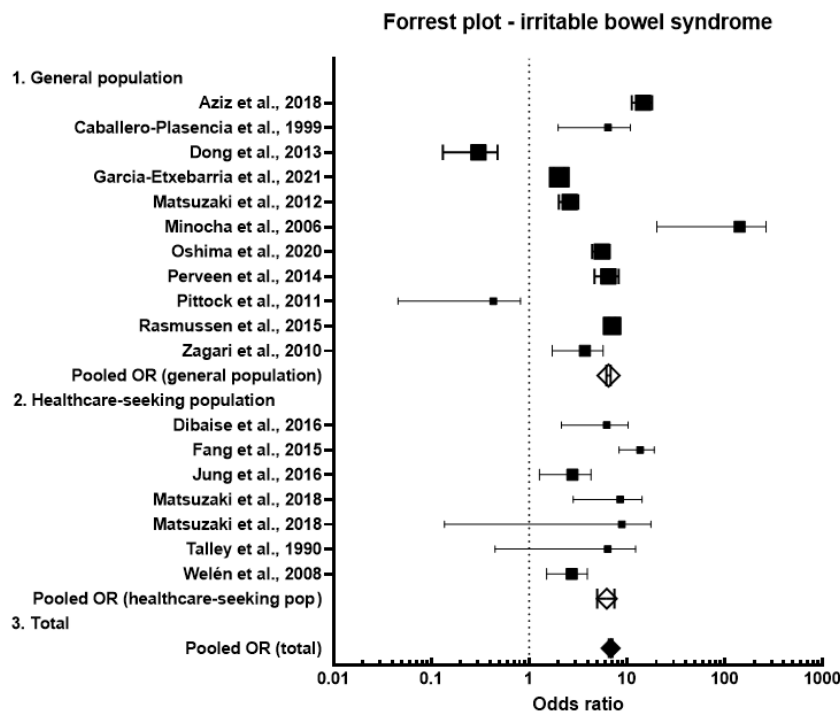


Figure 3.2. Forrest plot of odds ratios (OR) of the prevalences of irritable bowel syndrome in patients with functional dyspepsia vs controls.

3.7. Discussion

What have we learned from our work?

There is vast heterogeneity in the studies' setting, and the definitions of FD and comorbidities. We report the range of prevalences of numerous comorbidities and overlap syndromes reported in FD patients in the literature. We also synthesised the associations between FD and different comorbidities in comparison with controls to identify interplays between different conditions.

What does it teach us about the pathophysiology of functional dyspepsia?

Highlighting an association with some organic diseases makes it possible to clarify the link with these diseases or to consider the disease as organic dyspepsia (*H. pylori* gastritis, diabetes mellitus, etc.) but also to provide elements in favour of some pathomechanisms involved (dysimmunity, atopy, neuromuscular alterations, etc.). The frequency of overlaps with other DGBI raises the question of the mechanisms of these associations, particularly of a common aetiology to some of them. Many disorders belonging to the spectrum of central sensitivity syndromes are reported in FD patients. However, the presence of central sensitisation has never been assessed in FD, unlike IBS (Midenfjord et al., 2021). Finally, the frequency of association with various psychological factors suggests their importance in the pathophysiology of the disease.

What are the gaps in knowledge about comorbidities and overlap syndromes in functional dyspepsia?

No data is available about the overlap with MCAS, gastric or supragastric belching disorders, fibromyalgia syndrome, temporomandibular joint disorder, whiplash-associated disorders, myofascial pain syndrome, multiple chemical sensitivity syndrome, postural orthostatic tachycardia syndrome (POTS), restless leg syndrome, chronic pelvic pain syndrome, vulvodynia, premenstrual tension syndrome, alexithymia, attention-deficit/hyperactivity disorder (ADHD) in FD patients, among others. Population-based studies with control groups are needed to assess the association of those comorbidities in FD patients.

3.8. Conclusion

Functional dyspepsia can overlap with a wide range of comorbidities and overlap syndromes: organic diseases, other DGBI, non-GI functional somatic disorders, and psychological factors. The clinician should be familiar with the most frequent associations to help identify them in his practice. Future research is needed to assess the overlap with some comorbidities for which there is a lack of

Chapter 3

evidence in FD, to understand the pathophysiology underlying these associations and to determine their impact on the results of clinical trials.

3.9. Concluding paragraph

Summary of the main findings

- 5,131 references were identified, of which 250 were kept for analysis.
- Different comorbidities have been reported in patients with FD:
 - Organic diseases (*H. pylori* gastritis, diabetes mellitus, lactose intolerance, etc.);
 - Other DGBI (GORD, IBS, etc.);
 - Non-GI functional somatic disorders (CFS, migraine, etc.);
 - Psychological factors (anxiety, depression, sleep disorders, etc.).

Inferences

- Numerous overlaps and comorbidities have been reported in association with FD.
- Gaps in knowledge about comorbidities and overlap syndromes in FD were identified.
- Clues to underlying pathomechanisms of FD and overlaps in FD have been found: dysimmunity, atopy, neuromuscular alterations, common aetiology to different DGBI, central sensitisation, and psychological factors.

Perspectives

- Assess comorbidities and overlap syndromes not reported in the systematic review.
- Perform meta-analyses of prevalences for some comorbidities.

Dissemination

- None. The data presented in this chapter have not been submitted yet at the time of the printing of the manuscript.

Impact of the research

- None.



Chapter 4 METHODS USED FOR CLINICAL PROJECTS

DIFFERENT TOOLS HAVE BEEN USED for the clinical projects and are detailed in this chapter. A summary of the scores used and their validation or not in patients with DGBI and French language is shown in Table 4.1.

Table 4.1. Overview of the scores used in our clinical works.

Score	Number of items	Validation study		
		in FD patients?	in IBS patients?	in French?
<i>GIQLI</i>	36	yes	yes	yes
<i>HADS</i>	14	no	yes	no
<i>ISI</i>	7	no	no	yes
<i>PSQI</i>	19	no	no	yes
<i>R4DQ</i>	89	yes	yes	no
<i>TSS</i>	8	no	no	no

GIQLI: GastroIntestinal Quality of Life Index, HADS: Hospital Anxiety and Depression Scale, ISI: Insomnia Severity Index, PSQI: Pittsburgh Sleep Quality Index, R4DQ: Rome IV diagnostic questionnaire, TSS: Total Symptom Score.

4.1. Diagnosis and phenotyping of disorders of gut-brain interactions

Disorders of gut-brain interactions are diagnosed by the chronic occurrence and maintenance of defined symptoms in the absence of an organic disorder explaining the patient's complaints. Experts in the field regularly update definitions of these disorders that should be used in research, known as the Rome criteria. Successive Rome criteria have been published (Rome I in 1994 (Talley et al., 1991, Drossman et al., 1994), Rome II in 1999 (Talley et al., 1999b), Rome III in 2006 (Tack et al., 2006) and finally Rome IV in 2016 (Stanghellini et al., 2016)). This evolution in criteria is known as the Rome process. In our work, we used Rome III criteria for FD and IBS, and Rome IV criteria for FD, IBS and CNVS. The Rome III and Rome IV **diagnostic questionnaires** for functional GI disorders in adults (R3DQ and R4DQ), published by the *Rome Foundation for Disorders of Gut-Brain Interactions* (Thompson et al., 2006, Palsson et al., 2016), translate the diagnostic

criteria into questions. They were used to screen for DGBI among our cohort of patients according to the date of inclusion (before or after December 2017).

Assessing a patient's health, QoL and functional status, and, to a lesser extent, disease activity, is subjective. Therefore, tools designed to be used by the patient without the risk of misinterpretation of their answer by another person, especially a physician, have been developed. These measures of patient experience are termed "patient-reported outcomes" (PRO) in the context of clinical trials, and the tools used to measure them are "patient-reported outcome measures" (PROMs). Different instruments have been developed depending on their use in the general population (generic tools) or particular diseases (disease-specific tools), the latter being more responsive to change in clinical trials. These instruments are often used in tandem because they provide complementary information.

Patients referred to the Digestive Physiology Department in Rouen University Hospital were asked to complete a self-administered questionnaire collecting data on demographics, self-reported comorbidities, QoL, Rome diagnoses, and comorbidities, using validated scores for anxiety, depression, and sleep, among other things. Specialised nurses checked whether the questionnaires were correctly completed. All patients gave written informed consent for their data to be recorded and used for research in accordance with the Declaration of Helsinki, as revised in 2013 (World Medical Association, 2013). Approval was obtained from the data protection authority (Commission Nationale de l'Informatique et des Libertés, France; CNIL number 817.917), in compliance with the European Union General Data Protection Regulation (GDPR) law. Ethical approval for the data analysis was also obtained from the hospital ethics committee (Comité d'Éthique pour la Recherche non-Interventionnelle, CERNI) or a regional research ethics committee (Comité de Protection des Personnes Ile-de-France VII, CPP). The medical records were reviewed to exclude patients with organic diseases (diabetes mellitus, coeliac disease, IBD, history of surgery of the upper GI tract, *H. pylori* gastritis, etc.) and to select only patients fulfilling Rome criteria for the DGBI of interest.

4.2. Assessment of symptom burden in disorders of gut-brain interactions

The symptom burden can be assessed directly by measuring individual GI **symptoms' frequency or severity** (Veldhuyzen van Zanten et al., 1993, Vakil et al., 2016a). For example, a total score can be created by combining separate symptom scores, with higher scores representing a higher somatic symptom burden. Validated instruments are also available, like the Gastrointestinal Symptom Rating Scale (GSRS) (Svedlund et al., 1988) and tools assessing dyspeptic symptoms, more precisely: the Glasgow Dyspepsia Severity Score (GDSS) (el-Omar et al., 1996), the Leeds Dyspepsia Questionnaire (LDQ) (Moayyedi et al., 1998), the Nepean Dyspepsia Index (NDI) (Talley et al., 1999a), the Dyspepsia Symptom Severity Index (DSSI) (Leidy et al., 2000), the Severity of Dyspepsia Assessment (SODA) (Rabeneck et al., 2001), etc. Dyspeptic symptoms can also be assessed daily using the validated Leuven Postprandial Distress Scale (LPDS) (Carbone et al., 2016) or similar symptom diaries.

Similarly, different questionnaires are available to assess the **severity of somatic symptoms**, or somatisation: the Patient Health Questionnaire (PHQ)-15 (Kroenke et al., 2002), and its modified version PHQ-12, in which the three GI-related questions have been excluded (Spiller et al., 2010). The Somatic Symptom Scale-8 (SSS-8) is an even short version but needs to be validated in French (Gierk et al., 2014). It is recommended to use the term "multiple physical symptoms" instead of somatisation when using those scales to avoid the 'psychologization' of physical complaints (Crombez et al., 2009). Somatisation has not been assessed in our work. Still, a mediation analysis was performed in the study about PBS/IBS overlap (see Chapter 8) to determine the impact of psychological distress on the associations between different comorbidities.

The symptom burden can also be assessed indirectly by measuring **healthcare utilisation** (consulting behaviour [frequency of doctor visits per year, either for FD or for any health problems], number of previous surgical procedures, number of prescriptions and use of over-the-counter medications), **ability to work** and **QoL** (Vakil et al., 2016a, Sperber et al., 2021, Kovacs et al., 2022). Disability-adjusted life years (DALY), a measure of the number of years of healthy life lost due to illness and disability, could also be used (DALYs and Collaborators, 2017).

The presence and severity of eight digestive symptoms (postprandial fullness, abdominal pain, bloating, regurgitations, nausea, early satiation, belching and vomiting) in the 15 days before completing the questionnaire were collected prospectively using a 5-point Likert scale in our work. These symptoms were chosen because they are regularly reported in the literature (Revicki et al., 2004, Corsetti et al., 2004, DiBaise et al., 2016b). We constructed a *Total Symptom Score* (TSS) by summing up separate symptom scores, with higher scores representing a higher symptom burden.

4.3. Assessment of comorbidities in disorders of gut-brain interactions

Data about comorbidities was also collected.

Symptoms of **GOR** were defined as feelings of heartburn, regurgitations, or chest pain at least twice a week for more than six months. According to Rome criteria, evidence of GORD (abnormal acid exposure and symptom reflux association) would have required at least 24-hour pH monitoring or 24-hour pH/impedance monitoring (Aziz et al., 2016), which was not available for all patients in our cohort. No validated GORD questionnaire was used in our work.

Anxiety and depression levels were assessed using the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983). Each subscale included seven items scored from zero to three. The higher the score, the higher the anxiety or depression levels. A diagnosis of anxiety or depression was defined by a corresponding subscale greater or equal to 11, as proposed in the original publication (Zigmond and Snaith, 1983). In contrast, the mixed anxiety-depressive disorder was defined by a total score greater or equal to 19. Optimal cut-off values of HADS subscales for screening for anxiety and depression in IBS patients are greater or equal to eight (Snijders et al., 2021). Other screening instruments for depression and anxiety are the PHQ-9 (Spitzer et al., 1999) and the Generalised Anxiety Disorder 7-item (GAD-7) (Spitzer et al., 2006) scales, respectively. The most widely used screening tool is the HADS, but combining the PHQ-9 with the GAD-7 could better assess anxiety and depression separately (Boeckxstaens et al., 2016).

Gastrointestinal-specific anxiety, assessing the fear of GI symptoms, has been shown to influence symptom severity and QoL in IBS patients (Labus et al.,

2007). The Visceral Sensitivity Index (VSI) is a validated tool for determining GI-specific anxiety (Labus et al., 2004) but has not been assessed specifically in FD.

Sleep was evaluated using two different questionnaires. The Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989) was used to assess sleep quality. The PSQI score ranges from zero to 21. The higher the score, the worse the sleep quality. Altered sleep quality was defined by a PSQI greater than five, with a sensitivity of 89.6% and a specificity of 86.5% (Buysse et al., 1989). The PSQI score comprises seven component scores (subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleeping medication, and daytime dysfunction), each weighted zero to three points. The Insomnia Severity Index (ISI) (Bastien et al., 2001) was used to assess insomnia. Insomnia was defined by an ISI score greater or equal to ten, with a sensitivity of 86.1% and a specificity of 87.7% (Morin et al., 2011). Different categories can be individualised based on the results: no clinically significant insomnia (0-7 points), subthreshold insomnia (8-14 points), moderately severe clinical insomnia (15-21 points), and severe clinical insomnia (22-28 points).

Bladder pain syndrome was defined using an eight-item symptom-based self-questionnaire based on the ESSIC criteria published in 2008 (van de Merwe et al., 2008) (see Supplementary Table 5.1 in Addendum 5. Supplementary data for Article 5). All patients had to meet at least three criteria to be diagnosed with BPS: (1) pain, pressure or discomfort perceived to be related to the urinary bladder, (2) the presence of symptoms for at least six months, and (3) persistent or intermittent urge to void, pollakiuria (superior to eight mictions per day) or nycturia (at least one miction per night).

We assessed self-reported **migraine** in our work. The Women Health Study (WHS) taught us that a diagnosis of migraine was confirmed in 81.6-87.7% of questionnaire-based self-reported migraine cases (Schurks et al., 2009, Qiu et al., 2013) when applying the revised 2004 International Headache Society (IHS) criteria for migraine (ICHD-II) (Headache Classification Subcommittee of the International Headache Society, 2004). The WHS was a RCT designed to test low-dose aspirin and vitamin E to prevent cardiovascular disease and cancer among US female health professionals, with 39,976 women aged ≥ 45 years included throughout the USA and Puerto Rico from 1992 to 2004 (Ridker et al., 2005).

We assessed self-reported **fibromyalgia** in our work. The diagnosis of fibromyalgia in cohort studies is usually based on specific questionnaires, the

most commonly used being the Fibromyalgia Rapid Screening Tool (FiRST questionnaire). When using this six-item tool in people with diffuse pain for > 3 months, a score equal to or greater than 5 (each positive item = 1 point) detects fibromyalgia with a sensitivity of 90.5% and a specificity of 85.7% (Perrot et al., 2010). Self-reported fibromyalgia has also been used in other studies with success, however (Sleurs et al., 2020).

Finally, some patients were also asked to self-report **chronic fatigue**.

4.4. Assessment of quality of life in disorders of gut-brain interactions

Disorders of gut-brain interactions are non-life-threatening. Their treatment is, therefore, not aimed at a gain in terms of survival. Still, it has another health objective: to minimise their physical, psychological and social repercussions, or, in other words, to improve the QoL of these patients. Quality of life is a concept for which there is no consensus definition. It involves different dimensions: physical (physical capacity, autonomy, activities of daily living, etc.), psychological (emotionality, anxiety, depression, etc.), somatic (pain, fatigue, sleep, etc.) and social (family, professional and friendship environments, participation in leisure activities, sexual life, etc.). Health-related QoL focuses on the aspects of overall QoL which can affect perceived physical and mental health. Quality of life and HR-QoL are used interchangeably in our studies.

Although the concept is difficult to define, many measuring instruments are available. These are scales in the form of self-questionnaires. There are two types of questionnaires: generic questionnaires, which are designed to assess a general population, and specific questionnaires, which are oriented on a disease.

The most classical **generic questionnaire** is the Medical Outcome Study - Short Form 36 items (SF-36) (Ware and Sherbourne, 1992). It has 36 questions covering eight dimensions of health: physical activity, limitations due to physical condition, physical pain, life and relationships with others, mental health, limitations due to mental state, vitality, and perceived health. The scores for each dimension can be aggregated into physical and mental scores; this instrument has no overall QoL score. There is also a shorter version, the Short form-12 score (SF-12). The EuroQol-5 dimension (EQ-5D™) from the EuroQol group (© 2009 EuroQol Group), another generic questionnaire, is also a valid instrument for measuring

QoL in FD patients (Mahadeva et al., 2009). The module about QoL from the Patient-Reported Outcomes Measurement Information System (PROMIS) Global-10 questionnaire has also been used to assess QoL in FD (Sperber et al., 2021).

Disease-specific questionnaires are also available in FD: the Patient Assessment of upper GastroIntestinal disorders – Quality Of Life (PAGI-QOL) (de la Loge et al., 2004), designed to assess QoL in upper GI disorders (dyspepsia, GOR and gastroparesis), the Short Form – Nepean Dyspepsia Index (SF-NDI) (Talley et al., 2001b), the Quality of Life in Reflux and Dyspepsia (QOLRAD) questionnaire (Wiklund et al., 1998), etc.

A scale already developed and validated in another country and another language cannot be transcribed by simple translation. It is necessary to ensure a faithful cultural adaptation, which implies validation in the new language, since the translation is more conceptual than literal. Indeed, the socio-cultural context partly conditions the values given to the different dimensions explored. For example, references to professional life, hobbies, sexuality and religion differ from one society to another. It is, therefore, essential to ensure that a questionnaire is validated in the population and the language studied.

Given that we studied FD, but also the different comorbidities associated with it, and in a French population, we chose a QoL questionnaire validated in French and for various GI disorders, the GastroIntestinal Quality of Life Index (GIQLI) (Slim et al., 1999). This score is composed of 36 items related to five domains: symptoms (19 items), physical state (7 items), emotional function (5 items), social integration (4 items), and the effect of treatment (1 item). The global score ranges from 0 to 144. The higher the score, the better the QoL.

4.5. Assessment of gastric emptying

Different techniques to assess GE have been described, the most commonly used in clinical practice being scintigraphy and breath tests (Szarka and Camilleri, 2009).

Estimating GE is based on a simplistic **physiological model**, considering that the fundus plays a role in the emptying of liquids by increasing fundic pressure, and in the reserve of solids, while the antrum plays a role in the crushing of solids and their evacuation. The fraction of liquids evacuated per unit of time is considered proportional to the instantaneous gastric content. The emptying of

solids is more complex. It begins by grinding the meal until it is reduced to particles of about one mm³. During this period, called the lag phase, the solid content of the stomach does not vary, and the curve shows a plateau. Gastric peristalsis then evacuates solids at a substantially constant speed during the emptying phase. However, the stomach does not function autonomously but depends on several neural, humoral and hormonal regulatory factors.

Mathematically, GE can be modelled using an exponential model for liquid emptying, a linear model for the terminal phase of solid emptying, or a modified power exponential function for the entire solid phase (Siegel et al., 1988). The formula of a power exponential function has the form of $y(t) = 1 - (1 - e^{-kt})^\beta$, where $y(t)$ is the fractional meal retention at time t , k is the GE rate in min⁻¹, t is the time interval in minutes, and β is the extrapolated y-intercept from the terminal portion of the curve, as shown in Figure 4.1 (Siegel et al., 1988). A value of $\beta > 1.0$ indicates an initial delay in emptying, while a value of $\beta < 1.0$ indicates an initial rapid emptying (Siegel et al., 1988). The two most common analyses are the lag phase, the duration of the plateau before the beginning of the evacuation, and the T½, the evacuation half-life of the phase considered. When using the power exponential model, a parameter which accounts for the lag phase is given for solids in addition to the T½. The lag phase is expressed by the formula $T_{LAG} = \ln \frac{\beta}{k}$ (Siegel et al., 1988).

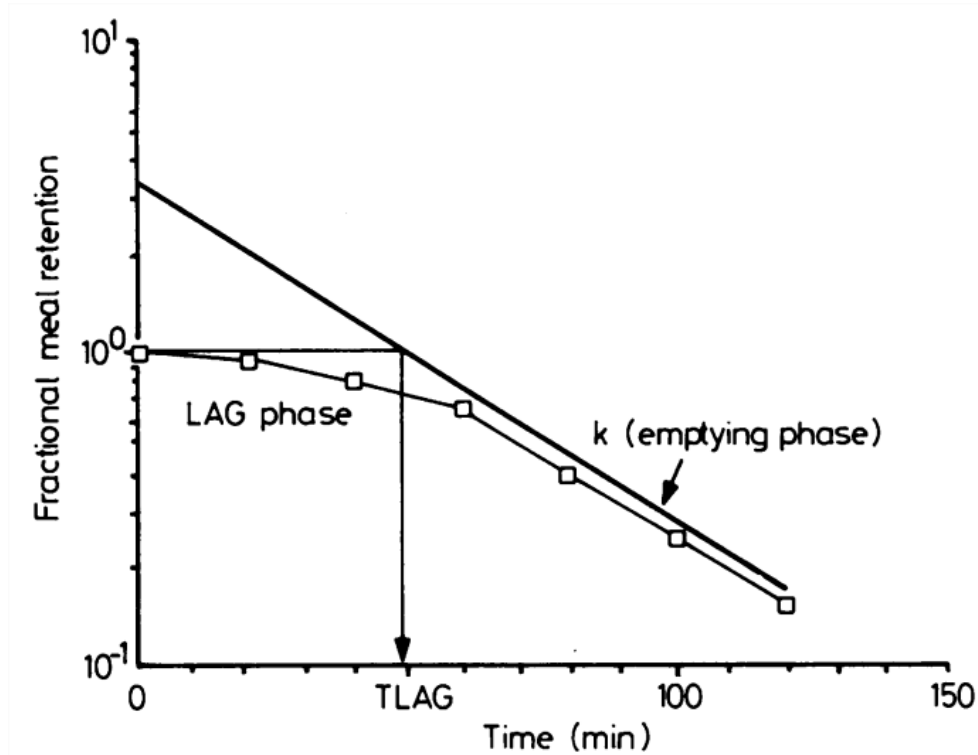


Figure 4.1. Typical emptying curve for solids showing the two phases of gastric emptying.

The emptying of solids is composed of an initial lag phase (T_{LAG}) and the emptying phase (k is the emptying rate).

Reproduced from Siegel JA et al. (Siegel et al., 1988). Copyright © 1988 BMJ Publishing Group Ltd. & British Society of Gastroenterology.

The **meal** offered to the patient must be physiological. Given the constant caloric flow through the pylorus ($\sim 8 \text{ kJ} \cdot \text{min}^{-1}$), the GE time increases with the meal's caloric content. There must be a compromise between reducing the caloric content to make the examination shorter and, therefore, more manageable for the patient, and having a sufficiently high caloric content to limit measurement errors and the effect of interindividual variations and, therefore, have better measurement accuracy. The meal's composition includes solid and liquid phases, which must respect a good balance between carbohydrates, lipids and proteins. A breakfast meal (445 kcal), including a solid phase with two eggs, two slices of white bread and butter, and a liquid phase consisting of 300 mL of water, is

typically used. The examination is carried out after an overnight fasting period of at least six hours, at breakfast time, and drugs likely to interfere with GE are discontinued for at least 48 hours.

Gastric scintigraphy of solids $\pm$ liquids is considered the reference method to assess GE. It uses a standardised protocol (Abell et al., 2008). The principle involves measuring radiation emitted by radiolabelled components of gastric contents at regular intervals. Dual-labelled meals are composed of an egg-white marked with technetium colloids (colloidal sulphur doped with ^{99m}Tc) and a liquid phase with ^{111}In -labelled diethylenetriamine pentaacetate (DTPA). Other radiotracers have also been described for solid phase assessment (^{99m}Tc -phytate (Mat Nawi et al., 2020) and ^{99m}Tc -DTPA). ^{99m}Tc in vivo labelled chicken liver has also been used in the past instead of ^{99m}Tc -labelled egg. However, some patients cannot ingest the solid phase, and only results for liquid emptying are available. Recently, a procedure based on a 400 mL “Nottingham Test Meal”, composed of 200 mL Vanilla Fortisip (Nutricia Ltd) mixed with 200 mL of water and a radiolabel (^{99m}Tc -DTPA or ^{111}In -DTPA), was demonstrated to be well tolerated by 98% of non-diabetic dyspeptic patients referred for the scintigraphy (Hay et al., 2022).

As the radioisotopes emit gamma photons, the intragastric radioactivity measured using a gamma camera is assimilated to the volume of food content in the stomach at any time. External counting of the residual radioactivity emanating from the stomach at regular intervals makes it possible to deduce the gastric transit of food. The acquisition duration must be greater than the $T_{1/2}$ to avoid extrapolating the data; in practice, four hours is recommended for gastric scintigraphy (Abell et al., 2008).

The results are expressed in the form of a decreasing curve of the radioactivity as a function of time and for each tracer. Delayed GE for solids is currently defined as total gastric retention of at least 10% of the ingested meal based on the 4-hour value.

The scintigraphy technique is a physiological, reliable, and non-invasive method that is well-accepted by patients. A liquid meal can be used in patients intolerant to solid meals. It allows the emptying of liquids and solids to be studied separately, as well as the emptying of the proximal and the distal parts of the stomach. Limitations include its cost, duration and exposure to ionising radiation.

The alternative to GE scintigraphy is a stable isotope (carbon-13 or carbon-14) **breath testing** (Keller et al., 2021). The tests using carbon-13 are

favoured since they are non-ionising. Assessment of GE for solids in adults using ^{13}C -octanoic acid breath testing was first described in 1993 by Ghoo et al. (Ghoo et al., 1993). The principle of the test is that the rapid absorption of the carbon-13-labelled octanoic acid, a medium-chain fatty acid, in the duodenum is followed by the oxidation of ^{13}C -octanoic acid to ^{13}C -carbon dioxide ($^{13}\text{CO}_2$) in the liver, and then by the elimination of the $^{13}\text{CO}_2$ by the lungs, as shown in Figure 4.2A. Since the post-gastric stage is relatively constant, the time to the appearance of $^{13}\text{CO}_2$ in the exhaled air is therefore correlated with the evacuation time of solids from the stomach to the duodenum. In practice, after an overnight fasting period, subjects ingest a test meal with a caloric value of 250 kcal, consisting of two slices of bread and an egg whose yolk has been cooked separately from the white after incorporating ^{13}C -octanoic acid. The use of muffins or pancakes labelled with ^{13}C -octanoic acid has also been proposed (Chey et al., 2001, Huang et al., 2023). Expired air samples are collected classically every 15 minutes for four hours.

The results are expressed in the form of a curve showing the percentage of $^{13}\text{CO}_2$ exhalation of the given ^{13}C per period of time, as shown in Figure 4.2B, or, alternatively, the percentage of the cumulative ^{13}C dose exhaled. The $T_{1/2}$ is calculated from that curve using the formula $T_{1/2} = \frac{-1}{k} \ln(1 - 2)^{\frac{-1}{\beta}}$ (Ghoo et al., 1993). The lag phase corresponds to the time to obtain the peak of $^{13}\text{CO}_2$ exhalation and is calculated using Siegel's formula (Siegel et al., 1988). A third parameter, the GE coefficient (GEC), an index of the GE rate, was originally calculated by Ghoo et al. but is not widely used (Ghoo et al., 1993). The same research team later published a model separating the emptying rate of solids from ingestion to the pylorus, correcting for the postgastric processing of octanoic acid (Maes et al., 1998). In this model, the $T_{1/2}$ can be calculated by solving the equation $\int_0^{T_{1/2}} M(t)dt = \frac{1}{2} \int_0^{\infty} M(t)dt$, a continuous function where $M(t)$ is the emptying rate of the labeled solids from mouth to pylorus (Maes et al., 1998).

A cut-off for $T_{1/2}$ of 166 minutes is used to discriminate patients with delayed GE of solids if the classical test meal is used (Bromer et al., 2002). Other cut-offs have been published with other meals. For example, a cut-off for $T_{1/2}$ of solids of 109 minutes is used when pancakes (250 kcal) are given to evaluated subjects (Huang et al., 2023). The calculated $T_{1/2}$ has an excellent correlation with the $T_{1/2}$ obtained by scintigraphy (Maes et al., 1998).

Chapter 4

This test is reliable, inexpensive, and does not expose individuals to ionising radiation if carbon-13 is used as a marker. This test is also sensitive enough to detect changes in GE induced by drugs (Maes et al., 1994). However, it does assume normal small bowel absorption and liver and pulmonary functions.

Carbon-13-labelled *Spirulina platensis*, a blue-green algae, is also used to label solids in the USA (Szarka et al., 2008), and ^{13}C -acetate or ^{14}C -glycin can be used for liquids (Braden et al., 1995).

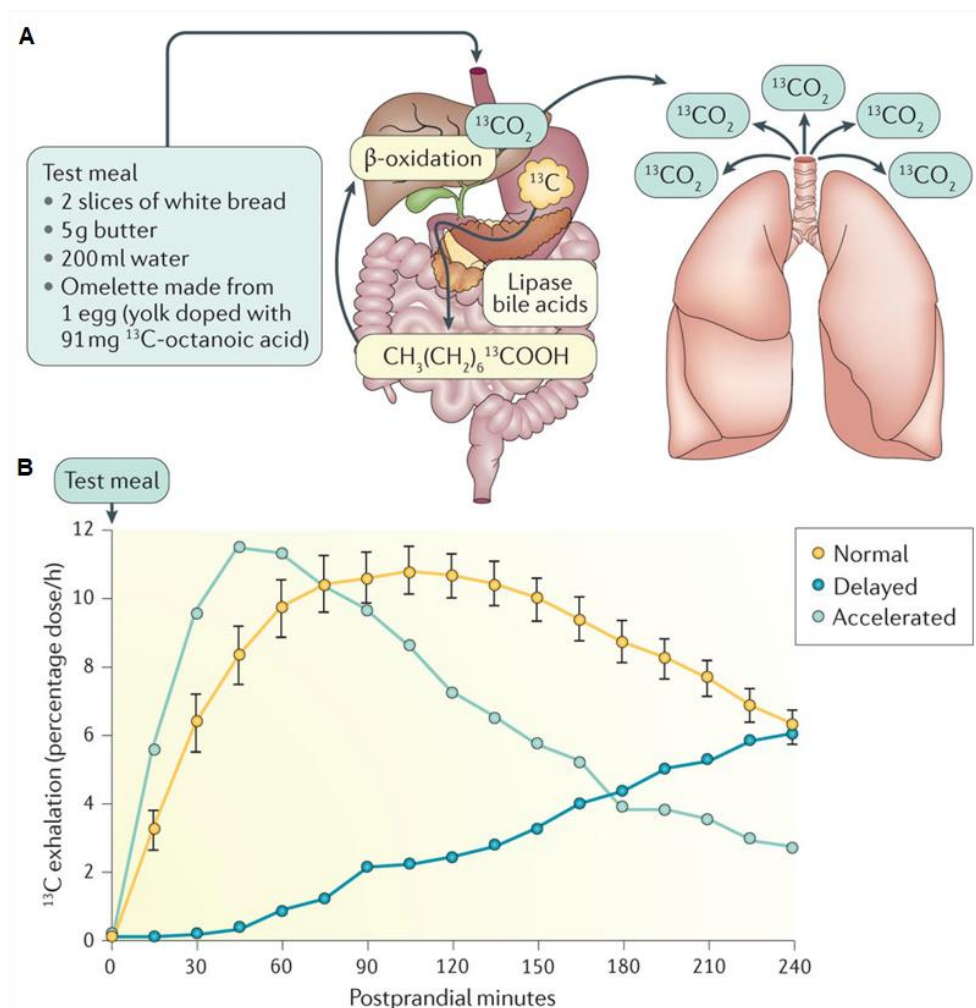


Figure 4.2. Carbon-13-labelled octanoic acid breath testing.

(A) ^{13}C -octanoic acid is rapidly absorbed in the duodenum after gastric emptying, and transported to the liver, where its metabolism leads to the production and then exhalation of $^{13}\text{CO}_2$. (B) Examples of values for accelerated, normal and delayed gastric emptying are shown. Normal data are shown as mean $\pm$ standard error of the mean.

Adapted from Keller J et al. (Keller et al., 2018). Copyright © 2018 Jutta Keller, Gabrio Bassotti, John Clarke, Phil Dinning, Mark Fox, Madhusudan Grover, Per M. Hellström, Meiyun Ke, Peter Layer, Carolina Malagelada, Henry P. Parkman, S. Mark Scott, Jan Tack, Magnus Simren, Hans Törnblom & Michael Camilleri on behalf of the International Working Group for Disorders of Gastrointestinal Motility and Function.

Other methods to assess GE include polyethylene glycol (PEG) dilution (Naslund et al., 2000), real-time ultrasonography (Duan et al., 1993) with repeated measurements of the antral area (Darwiche et al., 1999), magnetic resonance imaging (MRI) (Bertoli et al., 2022, Bertoli et al., 2023), and absorption tests with acetaminophen (Naslund et al., 2000) or sulphamethizole (Suzuki et al., 1999). Using ultrasound is operator-dependent. However, it requires geometric assumptions and generally only measures liquid emptying. The acetaminophen absorption test is based on the fact that acetaminophen diluted in water is rapidly absorbed at the duodenal level. The iterative dosage of plasmatic acetaminophen makes it possible to determine the pharmacokinetic parameters correlated with liquid emptying scintigraphy. The test requires normal small bowel absorption and repetitive blood sampling, however.

The gastric transit time can also be assessed using radiopaque markers, capsule endoscopy, magnetic capsules or wireless motility capsules (SmartPill®) (Diaz Tartera et al., 2017). Other methods can be used to determine gastric volume and content, such as single-photon emission computed tomography (SPECT) (De Schepper et al., 2004). Still, these are outside the scope of this chapter.



Chapter 5 ARTICLE 2. STUDY OF SLEEP DISTURBANCE AND QUALITY OF LIFE IN FUNCTIONAL DYSPEPSIA

5.1. Introductory paragraph

Articulation with previous projects

Sleep disturbance is frequent in patients with FD. Among the comorbidities associated with FD, revealed in our systematic review, we considered sleep disorders of particular interest because it allowed us to study the causal links between comorbidities and the disease. Indeed, the associations between different comorbidities and FD are chicken and egg situations: it is difficult to know which of the two existed first and which caused the other one. The association with sleep disorders could be a model to assess where the association comes from. Gastro-oesophageal reflux, in particular, is suspected of playing a role in the development of sleep disturbances in FD patients, which shows the complexity underlying the associations with comorbidities in DGBI. Furthermore, it enabled us to characterise altered sleep in FD and assess factors influencing QoL in this disorder.

What is already known?

Sleep disturbance and altered QoL are common in FD patients.

Research questions

- What are the prevalences of poor sleep quality and insomnia in FD?
- Which factors are associated with sleep disturbance in FD?
- Is sleep disturbance a determinant of poor QoL in FD?

Aims

- Assess the relationship between subjective sleep and QoL.
- Identify factors associated with poor sleep in FD.

Chapter 5

Methodology

- Population: 1,220 patients referred for DGBI at a single tertiary care centre (end 2017 - June 2019)
 - Rome IV-based FD
 - 355 patients kept for analysis
- Self-administered questionnaire
 - Sleep: PSQI & ISI
 - Severity of dyspeptic symptoms: composite score (Total Symptom Score or TSS)
 - Quality of life: GIQLI
 - Anxiety and depression: HADS

My contribution

I designed the study, contributed to the analysis and interpretation of the data, drafted the manuscript, and reviewed the manuscript critically for important intellectual content.

5.2. Title page

Complete title

Sleep quality and insomnia are associated with quality of life in functional dyspepsia

Short title

Sleep in functional dyspepsia

Authors

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5.3. Abstract

Background/Aims

Sleep disturbances are common in patients with functional dyspepsia. We aimed to assess the relationship between subjective sleep and quality of life and to identify factors associated with impaired sleep in functional dyspepsia.

Methods

One thousand two hundred twenty patients referred for functional gastrointestinal disorders at a single tertiary care centre between the end of 2017 and June 2019 were studied using a self-administered questionnaire. Three hundred fifty-five patients with Rome IV-based functional dyspepsia were identified. Sleep was assessed using both the *Pittsburgh Sleep Quality Index* (PSQI) and the *Insomnia Severity Index* (ISI). The severity of dyspeptic symptoms was assessed using the *Total Symptom Score* (TSS). Quality of life was assessed by the *Gastrointestinal Quality of Life Index* (GIQLI). Anxiety and depression levels were evaluated using the Hospital Anxiety and Depression (HAD) scale.

Key results

Among the 355 patients with functional dyspepsia, 66 (18.6%) patients displayed normal sleep quality, whereas 289 (81.4%) patients had altered sleep quality. Functional dyspepsia patients with sleep disturbance were older (48.1 ± 15.4 vs 41.4 ± 16.0 , $p = 0.0009$), had decreased quality of life (GIQLI: 75.3 ± 18.5 vs 92.1 ± 15.4 , $p < 0.0001$), greater severity of their symptoms (TSS: 18.9 ± 3.6 vs 17.2 ± 3.9 , $p = 0.0007$), and higher anxiety and depression scores (HADS: 17.7 ± 7.2 vs 11.9 ± 5.1 , $p < 0.0001$). A correlation was found between sleep quality and quality of life ($r = -0.43$ [95% CI: -0.51 to -0.34], $p < 0.0001$). Independent factors predicting poor sleep quality were age (OR 1.03 [95% CI: 1.01-1.05], $p = 0.006$), depression level (OR 1.27 [95% CI: 1.16-1.39], $p < 0.0001$) and the severity of dyspeptic symptoms (OR 1.13 [95% CI: 1.04-1.22], $p = 0.004$).

Conclusions

A high prevalence of sleep disturbance was found in patients suffering from functional dyspepsia, with 81% having altered sleep quality and 61% having insomnia based on subjective assessment. Altered sleep quality and insomnia

Chapter 5

were associated with altered quality of life, higher severity of symptoms and higher anxiety and depression scores in this disorder.

5.4. Introduction

FUNCTIONAL DYSPEPSIA IS A DGBI affecting 7.2% of the general population in the Western world (Sperber et al., 2021), defined by upper digestive complaints (epigastric pain and/or burning, early satiation and/or postprandial fullness) lasting for more than six months with a negative workup according to the Rome committee (Stanghellini et al., 2016). In the general population, sleep disorders are frequent, are associated with upper and lower GI symptoms and predict impaired QoL (Cremonini et al., 2009). They are known to be even more frequent in patients with FD compared to controls (Fass et al., 2000, Lu et al., 2005, Lacy et al., 2011, Futagami et al., 2013a, Shimpuku et al., 2014, Li et al., 2018), affecting over half of the patients in a recent meta-analysis (Andreev et al., 2021). However, sleep disturbance is not independently associated with FD in the general population (Vege et al., 2004). Sleep disorders are associated with symptom severity and higher levels of anxiety and depression in FD patients (Lacy et al., 2011, Futagami et al., 2013a). Overlap with IBS with or without NERD even worsens sleep quality in FD patients (Futagami et al., 2013b, Kim et al., 2018b). Patients with FD symptoms also experience more daytime sleepiness (Morito et al., 2014, Wu et al., 2017b). Impaired sleep impacts the lives of patients with FD since it reduces work productivity and worsens economic loss in those patients (Matsuzaki et al., 2018). Finally, sleep disturbance is prognostic since lower baseline sleep disturbance was associated with improved dyspepsia scores over 3-6 months in a recent cohort study (Singh et al., 2022). However, the relationship between sleep disturbance and QoL has never been investigated in FD patients.

We aimed to assess Rome IV-based FD patients regarding sleep quality and insomnia, to compare dyspeptic patients with normal vs altered sleep quality, to determine the relationship between subjective sleep and QoL, and to identify factors associated with altered sleep quality and insomnia in FD.

5.5. Materials and methods

This study is based on a retrospective analysis of prospectively acquired data from Rouen University Hospital. All patients had given written informed consent for data to be recorded and used for research, in accordance with the Declaration of Helsinki as revised in 2013 (World Medical Association, 2013).

Approval was obtained from the French data protection authority (Commission Nationale de l'Informatique et des Libertés, CNIL No 817.917), in compliance with French legislation. Ethical approval for the data analysis was obtained (CERNI No E2021-45).

Patients

We retrospectively analysed all patients referred to our centre for DGBI between December 2017 and June 2019 who completed a self-administered questionnaire. The medical records were reviewed to exclude patients with organic illnesses (diabetes mellitus, coeliac disease, IBD, history of surgery of the upper GI tract, *H. pylori* gastritis, etc.). Duplicates were also excluded. Only patients fulfilling Rome IV criteria for FD were kept for analysis.

Diagnostic criteria and assessment of patients' characteristics

Functional dyspepsia, PDS and EPS subtypes, and IBS were defined according to Rome IV criteria (Stanghellini et al., 2016, Lacy et al., 2016). Post-infectious origin of dyspeptic complaints was evaluated by asking for an episode of acute gastroenteritis during the month preceding the onset of symptoms (Parkman et al., 2010). Eight dyspeptic symptoms (postprandial fullness, bloating, abdominal pain, regurgitations, nausea, early satiety, belching and vomiting) were collected using a 5-point Likert scale. Symptoms were graduated from 0 to 4 for the last 15 days, with 0 corresponding to absence and 4 to extremely severe. A TSS was used to evaluate dyspeptic symptom severity (McCallum et al., 2005) and was calculated by adding the eight individual symptoms' scores. The score ranges from 0 to 32, with higher scores reflecting more severe symptoms. Patients were also asked to report the duration of their dyspeptic symptoms (postprandial fullness, early satiation, and epigastric pain/burning). The GIQLI, a validated score in French (Slim et al., 1999), was used to measure QoL. This score comprises 36 items concerning symptoms, physical state, emotions, and social impact. The items are related to 5 dimensions: symptoms (19 items), physical function (7 items), emotional function (5 items), social integration (4 items), and the effect of any medical treatment (1 item). The global score ranges from 0 to 144; the higher the score, the better the QoL. Symptoms of GOR were defined as feeling

heartburn, regurgitations, or chest pain at least two times per week for more than six months. Anxiety and depression levels were also assessed, using the HADS and its subscales (Zigmond and Snaith, 1983). Each subscale includes seven items scored from 0 to 3: the higher the score, the higher the anxiety or depression levels. Patients were asked to self-report chronic fatigue. Gastric emptying was assessed by ¹³C-octanoic acid breath testing in a subgroup of patients, with the study protocol being explained in detail elsewhere (Wuestenberghs et al., 2019). A cut-off for the $T_{1/2}$ of 166 minutes was used to discriminate against patients with delayed GE (Bromer et al., 2002).

Evaluation of sleep

Sleep was assessed using the PSQI (Buysse et al., 1989) and the ISI (Bastien et al., 2001) questionnaires. The PSQI score ranges from 0 to 21; the higher the score, the worse the sleep quality. Altered sleep quality was defined as a PSQI greater than five (89.6% sensitivity and 86.5% specificity) (Buysse et al., 1989). The ISI score is composed of 7 component scores, each weighted 0 to 3 points. Insomnia was defined as an ISI score greater or equal to ten (86.1% sensitivity and 87.7% specificity) (Morin et al., 2011). Different categories were individualised based on the results: no clinically significant insomnia for 0-7 points, subthreshold insomnia for 8-14 points, clinical insomnia (moderate severity) for 15-21 points, and clinical insomnia (severe) for 22-28 points.

Study design & statistical analysis

Consecutive patients with dyspeptic complaints were screened for FD according to Rome IV criteria. After descriptive statistics of the entire population, FD patients with normal and altered sleep quality according to the PSQI threshold were compared for their characteristics, QoL and anxiety-depression scores. The same analyses were performed concerning insomnia using the ISI results. Quantitative data were expressed by mean and SD, and compared between subgroups using a non-gaussian unpaired t-test (Mann-Whitney test). Qualitative variables were, for their part, compared using Fisher's exact test. Multiple group comparisons were performed using the Kruskal-Wallis test with Dunn's multiple comparison post-test to compare all pairs of columns. The correlation between

sleep quality expressed by the PSQI and quantitative variables (GIQLI, TSS, BMI, HADS, etc.) was determined using the Pearson correlation coefficient.

Finally, additional analyses included the search for factors associated with altered sleep quality and insomnia and analysing of the influence of GE in a subgroup of patients. A multivariate binary logistic regression model was used to identify factors associated with altered sleep quality and insomnia, using backward Wald stepwise selection (entry probability 0.05 and removal probability 0.10). Adjusted OR and their 95% CI were calculated. "Altered sleep quality" and "insomnia" were used as the dependent variables. Age, BMI, duration of FD symptoms, gender, HADS-A and HADS-D subscales, overlap with IBS, smoking and TSS score were used as independent variables. Two-tailed p-values < 0.05 were considered statistically significant.

The data were extracted on spreadsheets using Microsoft Excel 365 for Windows (version 1903) and were analysed using GraphPad Prism version 5.03 for Windows (GraphPad Software Inc, San Diego, CA, USA, www.graphpad.com), except multivariate analysis, which was performed using SPSS software version 20.0.0 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp).

5.6. Results

Patient characteristics

One thousand two hundred and twenty patients referred during the study period were screened for inclusion. After excluding duplicates (n = 114) and patients not fulfilling Rome IV criteria for FD (n = 751), a total of 355 (29.1%) patients were analysed. Among them, 227 (63.9%) patients had a PDS subtype, 41 (11.6%) EPS subtype and 87 (24.5%) PDS+EPS overlap. A female predominance was present (76.6%). The mean age of the patients was 46.9 ± 15.7 years. The mean duration of FD symptoms was 6.4 ± 8.3 years. Overlaps with IBS and GOR symptoms were present in 159 (44.8%) and 181 (51.0%) patients, respectively. The clinical and demographic characteristics of the overall population are presented in Table 5.1.

Table 5.1. Patient characteristics of the overall population.

	Patients (n = 355)
<i>Median age, years (range)</i>	47 (18-83)
<i>Mean BMI, kg.m⁻² (± SD)</i>	24.1 (± 5.2)
<i>Sex ratio Male/Female (% women)</i>	0.3 (76.6)
<i>Smoking, n (%)</i>	60 (16.9)
<i>IBS, n (%)</i>	159 (44.8)
<i>Any GOR symptom, n (%)</i>	181 (51.0)
<i>Gastric half-emptying time, minutes (± SD)*</i>	164.4 (± 59.0)
<i>Delayed gastric emptying, n (%)*</i>	31 (39.7)
<i>Median duration of FD symptoms, months (range)</i>	36 (7-720)
<i>TSS, mean score (± SD)</i>	18.6 (± 3.7)
<i>GIQLI, mean score (± SD)</i>	78.4 (± 19.1)
<i>and its domains:</i>	
<i>symptoms, mean score (± SD)</i>	44.4 (± 8.8)
<i>physical function, mean score (± SD)</i>	11.4 (± 5.9)
<i>emotional function, mean score (± SD)</i>	10.0 (± 4.3)
<i>social function, mean score (± SD)</i>	9.4 (± 4.1)
<i>treatment, mean score (± SD)</i>	3.2 (± 1.2)
<i>HADS, mean score (± SD)</i>	16.6 (± 7.2)
<i>HADS-A, mean subscale (± SD)</i>	9.9 (± 4.2)
<i>HADS-D, mean subscale (± SD)</i>	6.7 (± 4.1)

BMI: body mass index, EPS: epigastric pain syndrome, FD: functional dyspepsia, GOR: gastro-oesophageal reflux, GIQLI: GastroIntestinal Quality of Life Index, HADS: Hospital Anxiety and Depression Scale, HADS-A and HADS-D: HADS Anxiety and Depression subscales respectively, IBS: irritable bowel syndrome, n: number, PDS: postprandial distress syndrome, SD: standard deviation, TSS: Total Symptom Score.

* Only available for a subgroup of 78 (22.0%) patients.

Altered sleep quality was present in 289 (81.4%) patients, while insomnia was present in 215 (60.6%). One hundred seventeen patients had taken at least one sleeping pill over the past month, whose 76 took sleep pills regularly. Chronic fatigue was self-reported by 139 patients (39.2%), with 92.8% of them presenting poor sleep quality compared to 74.1% of those without this complaint (OR 4.52 [95% CI: 2.22-9.20], $p < 0.0001$). Detailed characteristics of subjective sleep in our population are presented in Table 5.2.

Table 5.2. Detailed characteristics of subjective sleep in the overall population.

	Patients (n = 355)
Global PSQI, mean score ($\pm$ SD)	8.9 ($\pm$ 3.8)
PSQI component scores:	
<i>subjective sleep quality, mean score ($\pm$ SD)</i>	1.6 ($\pm$ 0.7)
<i>sleep latency, mean score ($\pm$ SD)</i>	1.7 ($\pm$ 1.0)
<i>sleep duration, mean score ($\pm$ SD)</i>	1.0 ($\pm$ 0.8)
<i>habitual sleep efficiency, mean score ($\pm$ SD)</i>	1.0 ($\pm$ 1.1)
<i>sleep disturbance, mean score ($\pm$ SD)</i>	1.6 ($\pm$ 0.6)
<i>use of sleeping medication, mean score ($\pm$ SD)</i>	0.8 ($\pm$ 1.2)
<i>daytime dysfunction, mean score ($\pm$ SD)</i>	1.2 ($\pm$ 0.9)
Altered sleep quality (PSQI > 5), n (%)	289 (81.4)
ISI, mean score ($\pm$ SD)	11.7 ($\pm$ 6.3)

Categories of insomnia:	
<i>no clinically significant insomnia, n (%)</i>	108 (30.4)
<i>subthreshold insomnia, n (%)</i>	126 (35.5)
<i>clinical insomnia (moderate severity), n (%)</i>	100 (28.2)
<i>clinical insomnia (severe), n (%)</i>	21 (5.9)
Insomnia (ISI ≥ 10), n (%)	215 (60.6)
ISI: Insomnia Severity Index, n: number, PSQI: Pittsburgh Sleep Quality Index, SD: standard deviation.	

Comparison between patients with and without sleep quality impairment

Patients with FD and altered sleep quality were older, had impaired QoL, greater severity of their symptoms, and higher anxiety and depression scores. On the contrary, BMI, gender, smoking, duration of FD symptoms, FD subtypes distribution, overlap with IBS, the reporting of GOR symptoms and GE rate were the same in both groups. Results are detailed in Table 5.3.

Table 5.3. Comparison of FD patients with normal vs altered sleep quality.

	Normal sleep quality (n = 66)	Altered sleep quality (n = 289)	p-value
Mean age, years ($\pm$ SD)	41.4 ($\pm$ 16.0)	48.1 ($\pm$ 15.4)	0.0009
Mean BMI, kg.m⁻² ($\pm$ SD)	23.2 ($\pm$ 4.4)	24.3 ($\pm$ 5.3)	0.11
Sex ratio Male/Female (% women)	0.3 (77.3)	0.3 (76.5)	> 0.99
Smoking, n (%)	7 (10.6)	53 (18.3)	0.2
IBS, n (%)	32 (48.5)	127 (43.9)	0.6

<i>Any reflux symptom, n (%)</i>	33 (50.0)	148 (51.2)	0.9
<i>Gastric half-emptying time, minutes ($\pm$ SD)*</i>	152.8 ($\pm$ 37.9)	166.5 ($\pm$ 61.8)	0.5
<i>Delayed GE, n (%)*</i>	4 (33.3)	27 (40.9)	0.8
<i>Mean duration of FD symptoms, months ($\pm$ SD)</i>	65.6 ($\pm$ 90.3)	78.6 ($\pm$ 101.8)	0.3
<i>TSS, mean score ($\pm$ SD)</i>	17.2 ($\pm$ 3.9)	18.9 ($\pm$ 3.6)	0.0007
<i>GIQLI, mean score ($\pm$ SD)</i>	92.1 ($\pm$ 15.4)	75.3 ($\pm$ 18.5)	< 0.0001
<i>GIQLI domains:</i>			
<i>symptoms, mean score ($\pm$ SD)</i>	48.2 ($\pm$ 8.1)	43.9 ($\pm$ 8.7)	0.004
<i>physical function, mean score ($\pm$ SD)</i>	15.7 ($\pm$ 5.1)	10.8 ($\pm$ 5.8)	< 0.0001
<i>emotional function, mean score ($\pm$ SD)</i>	12.2 ($\pm$ 3.6)	9.7 ($\pm$ 4.3)	0.0003
<i>social function, mean score ($\pm$ SD)</i>	11.6 ($\pm$ 3.4)	9.1 ($\pm$ 4.1)	0.0001
<i>treatment, mean score ($\pm$ SD)</i>	3.5 ($\pm$ 1.0)	3.2 ($\pm$ 1.2)	0.08
<i>HADS, mean score ($\pm$ SD)</i>	11.9 ($\pm$ 5.1)	17.7 ($\pm$ 7.2)	< 0.0001
<i>HADS-A, mean subscale ($\pm$ SD)</i>	7.8 ($\pm$ 3.5)	10.4 ($\pm$ 4.3)	< 0.0001
<i>HADS-D, mean subscale ($\pm$ SD)</i>	4.1 ($\pm$ 2.9)	7.3 ($\pm$ 4.1)	< 0.0001
<i>Global PSQI, mean score ($\pm$ SD)</i>	3.9 ($\pm$ 1.0)	10.1 ($\pm$ 3.3)	< 0.0001
<i>Altered sleep quality (PSQI > 5), n (%)</i>	0 (0.0)	289 (100.0)	< 0.0001
<i>ISI, mean score ($\pm$ SD)</i>	4.5 ($\pm$ 3.2)	13.4 ($\pm$ 5.7)	< 0.0001
<i>Insomnia (ISI $\geq$ 10), n (%)</i>	5 (7.6)	210 (72.7)	< 0.0001

BMI: body mass index, EPS: epigastric pain syndrome, FD: functional dyspepsia, GE: gastric emptying, GIQLI: GastroIntestinal Quality of Life Index, HADS: Hospital Anxiety and Depression Scale, HADS-A and HADS-D: HADS Anxiety and Depression subscales respectively, IBS: irritable bowel syndrome, ISI: Insomnia Severity Index, n: number, PDS: postprandial distress syndrome, PSQI: Pittsburgh Sleep Quality Index, SD: standard deviation, TSS: Total Symptom Score.

* Only available for a subgroup of 78 (22.0%) patients.

A correlation was found between sleep quality and QoL ($r = -0.43$ [95% CI: -0.51 to -0.36], $p < 0.0001$), each deterioration of 1 point in sleep quality assessed by the global PSQI being associated with a decrease of 0.43 point of QoL set by the GIQLI. Other parameters correlated with the sleep quality were age, BMI, anxiety and depression scales (HADS and its subscales), and symptom severity assessed by the TSS ($r = 0.21, 0.017, 0.37$ and 0.16 respectively, all with $p < 0.05$), but not the duration of FD symptoms or the $T_{1/2}$ ($r = 0.29$ and 0.20 respectively). Results are detailed in Addendum 2. Supplementary data for Article 2 (Supplementary Table 2.1) and depicted in Figure 5.1.

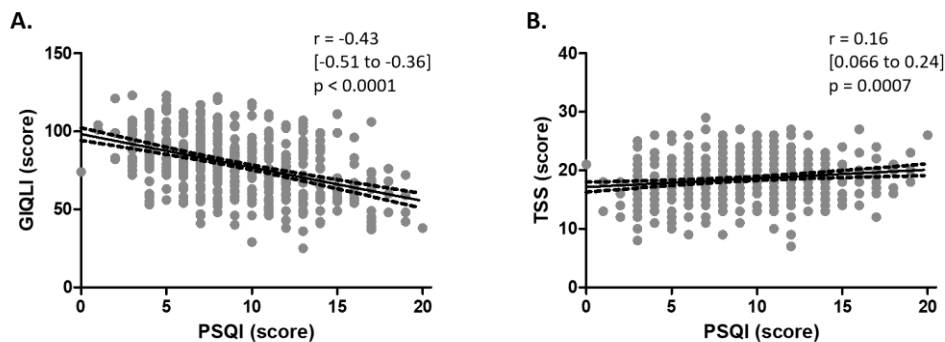


Figure 5.1. Correlation between the global PSQI and (A) the GIQLI and (B) the TSS. The regression line best predicting the model and its 95% confidence band are shown in both cases.

GIQLI: GastroIntestinal Quality of Life Index, PSQI: Pittsburgh Sleep Quality Index, TSS: Total Symptom Score.

Comparison between patients with and without insomnia

Patients with FD and insomnia had impaired QoL, greater severity of their symptoms, and higher anxiety and depression scores. On the contrary, age, BMI, gender, smoking, duration of FD symptoms, FD subtypes distribution, overlap with IBS and the reporting of GOR symptoms were the same in both subgroups, except chest pain which was more frequent in those with insomnia. Results are detailed in Addendum 2. Supplementary data for Article 2 (Supplementary Table 2.2).

The PSQI and ISI scores are highly correlated ($r = -0.41$ [95% CI: -0.50 to -0.32], $p < 0.0001$). Only 1 (0.5%) patient displayed insomnia without altered sleep quality among all patients presenting insomnia, whereas 79 (27.3%) patients showed altered sleep quality without insomnia among all patients presenting altered sleep quality.

Factors predicting altered sleep quality and insomnia in patients with functional dyspepsia

In multivariate analysis, predictive factors of poor sleep quality were age (OR 1.03 [95% CI: 1.01-1.05], $p = 0.006$), depression level assessed by the HADS-D subscale (OR 1.27 [95% CI: 1.16-1.39], $p < 0.0001$) and the severity of dyspeptic symptoms evaluated by the TSS (OR 1.13 [95% CI: 1.04-1.22], $p = 0.004$), while other factors (BMI, duration of the symptoms, gender, HADS-A, overlap with IBS and smoking) were not. The model combining age, depression score and symptom severity score correctly predicted poor sleep quality in 82.5% of the cases. Results are shown in Table 5.4.

Table 5.4. Multivariate binary logistic regression model of factors predicting altered sleep quality in FD patients.

	B	SE	OR	95% CI	p-value
Age	0.03	0.01	1.03	1.01-1.05	0.006
HADS-D	0.24	0.05	1.27	1.16-1.39	< 0.0001
TSS	0.12	0.04	1.13	1.04-1.22	0.004

Constant	-3.17	0.89	0.04		< 0.0001
B: unstandardised regression coefficient, CI: Confidence Interval, HADS-D: Hospital Anxiety and Depression Scale - Depression subscale, OR: odds ratio, SE: standard error, TSS: Total Symptom Score.					

Independent predictive factors of insomnia in our cohort were anxiety and depression levels assessed by the HADS-A and HADS-D subscales, respectively (OR 1.09 [95% CI: 1.02-1.16], $p = 0.01$ & OR 1.15 [95% CI: 1.07-1.24], $p < 0.0001$ respectively), while other factors (BMI, duration of the symptoms, gender, HADS-A, overlap with IBS, the severity of dyspeptic symptoms and smoking) were not. Results are shown in Table 5.5.

Table 5.5. Multivariate binary logistic regression model of factors predicting insomnia in FD patients.

	B	SE	OR	95% CI	p-value
HADS-A	0.08	0.03	1.09	1.02-1.16	0.01
HADS-D	0.14	0.04	1.15	1.07-1.24	< 0.0001
TSS	0.10	0.03	1.11	1.04-1.18	0.002
Constant	-3.11	0.67	0.05		< 0.0001
B: unstandardised regression coefficient, CI: confidence interval, HADS-A: Hospital Anxiety and Depression Scale - Anxiety subscale, HADS-D: Hospital Anxiety and Depression Scale - Depression subscale, OR: odds ratio, SE: standard error, TSS: Total Symptom Score.					

5.7. Discussion

We confirm the high prevalence of sleep disturbance in FD patients, with 81% having altered sleep quality based on subjective assessment and 61% having insomnia. For the first time, we show an association between altered sleep quality

or insomnia and altered QoL in FD patients. We also confirm that altered sleep quality is associated with higher symptom severity and anxiety and depression scores in FD. The same results were obtained using PSQI and ISI scores, considering that both scores were highly correlated. Our distribution pattern of FD subtypes is the same as reported in the literature (Aziz et al., 2018a). We confirm that sleep quality is comparable among the three subtypes of FD (PDS, EPS and PDS+EPS), as already shown by Yamawaki et al. (Yamawaki et al., 2014). The prevalence of IBS in our FD population was 45%, corresponding to the pooled prevalence of 37% (95% CI: 30-45) reported in a recent meta-analysis (Ford et al., 2010a).

An increased prevalence of sleep disturbance compared to healthy subjects is found in most studies concerning FD patients (Fass et al., 2000, Lu et al., 2005, Lacy et al., 2011, Futagami et al., 2013a, Shimpuku et al., 2014, Li et al., 2018) but is not consensual for IBS (Kim et al., 2018b, Koloski et al., 2021). However, the prevalence varies considerably among studies, depending on the definition used and the specific sleep disorder studied. Indeed, the ICSD-3 includes 83 conditions divided into seven main categories, the major disorder being insomnia (Sateia, 2014). The prevalence of sleep disturbance in patients with FD was 53.2% (95% CI: 37.7-68.4) in a recent meta-analysis (Andreev et al., 2021), with significant heterogeneity between the results ($p < 0.0001$). Sleep disorders were more frequent in FD patients than healthy controls, with an OR of 2.88 (95% CI: 2.52-3.30).

Patients with FD have decreased QoL (El-Serag and Talley, 2003). Known risk factors for impaired HR-QoL in FD are anxiety and depression (Haag et al., 2008), increasing age (Hantoro et al., 2018), female gender (Talley et al., 2006a), greater symptom severity (Haag et al., 2008), low-to-mid educational level (Hantoro et al., 2018), somatisation (Van Oudenhove et al., 2011b), greater overlap with other DGBI (Sperber et al., 2022), etc., but not GE (Talley et al., 2006a, Haag et al., 2010). Interestingly, amitriptyline has been shown to reduce the amount of REM sleep (Mertz et al., 1998a) and modestly improve sleep quality in dyspeptic patients (Herrick et al., 2018). Since we found a correlation between QoL and sleep quality in our cohort, sleep determinants should be considered among factors associated with QoL in this disorder. Furthermore, since altered sleep quality and insomnia are associated with altered QoL in FD patients, sleep could represent a target in future clinical trials in this disorder. Indeed,

altered sleep quality affects the prognosis of FD negatively (Yu et al., 2013, Chen et al., 2016, Singh et al., 2022). Recently, a non-randomised trial involving 20 patients suggested that adding sleep aids could improve GI symptoms and QoL in FD patients (Nakamura et al., 2021).

Mechanisms underlying the association between FD and altered sleep are poorly understood but are probably complex. Knowing if sleep disturbance is responsible for the occurrence of FD or is a consequence of the disorder is debated (Maneerattanaporn and Chey, 2009). Interestingly, difficulty falling asleep and altered sleep associated with worsening symptoms were independent risk factors for dyspepsia in a community-based cohort (Gathaiya et al., 2009), together with somatisation. It is logical to assume that digestive complaints could interact with sleep induction or continuation, but altered sleep could also increase symptoms perception by patients. Indeed, sleep deprivation decreased pain thresholds in healthy volunteers (Onen et al., 2001). Altered sleep could therefore exacerbate digestive complaints in these patients. This vicious circle could explain the association between altered sleep quality and higher symptom severity that we found in our work. Independent factors predicting altered sleep quality in FD patients in our study were age, depression levels and symptom severity. GORD is the most frequently reported factor involved in the pathogenesis of sleep alterations in FD. Indeed, sleep alterations tend to be aggravated by heartburn and regurgitation (Vakil et al., 2016b), and an antisecretory drug being shown to improve sleep in FD patients (Futagami et al., 2013a). Furthermore, patients with GORD overlapping with FD have more altered sleep quality than those with GORD alone (Lei et al., 2019a). Gastro-oesophageal reflux can awake patients or delay them falling asleep but can also induce brief arousals leading to fragmented sleep (Lacy et al., 2011). We didn't confirm a link between GORD and altered sleep in our study, probably because only GOR symptoms were assessed and not GORD. Moreover, the pathophysiology of sleep disturbance has been shown to involve alterations in rapid eye movement sleep (Kumar et al., 1992) and the ANS (Jarrett et al., 2008) in IBS; whether it is the same in FD remains to be determined. No relationship was found between sleep quality and GE rate in FD patients in our study, confirming the results of Futagami et al. (Futagami et al., 2013a). This is explained by the absence of effect of GE on oesophageal acid exposure (Gourcerol et al., 2013). Age seems not to explain the association between FD and altered sleep since there is no association between age and sleep quality in the general

population (Hinz et al., 2017). However, we found sleep disturbance to be associated with older age in our cohort. The presence of overlap with other DGBI could also play a role since patients with overlapping FD-IBS have greater sleep quality impairment than those with FD alone (Kim et al., 2018b). In addition, we did not find a correlation between the duration of FD symptoms and the quality of sleep. However, we found an association between sleep disturbance and greater severity of FD symptoms. Similarly, a Chinese study found that FD patients with sleep disorders had a higher morbidity rate than those who suffered from IBS or functional constipation (Zhao et al., 2018). Sleep disorders were already shown to be more frequent in refractory FD compared to non-refractory disease (Jiang et al., 2015). Finally, other psychological factors, like anxiety, depression and somatisation, could also induce sleep disturbance. Interestingly, a discrepancy between objective and subjective assessments of sleep quality has been reported in IBS patients, suggesting altered sleep perception in this disorder (Elsenbruch et al., 1999).

Limitations of our work include that it is retrospective, monocentric, and from a tertiary centre. Furthermore, we used a convenience cohort, representing only some of the FD population. Gastro-oesophageal reflux disease was not screened since no oesophageal pH monitoring was performed; only GOR symptoms are reported in our work. The use of sleep medication was not recorded, and we did not have a control group composed of healthy volunteers to compare our results with. Gastric emptying was only assessed in a subgroup of patients, with likely a selection bias. Somatisation was not evaluated, even if it could partly explain the association between FD and sleep dysfunction (Gathaiya et al., 2009). Another limitation is the use of self-reported sleep quality, using a questionnaire, instead of objective measures like polysomnography or actigraphy. Furthermore, the PSQI is known to be influenced by psychological factors, especially depression state (Buysse et al., 1989). Higher anxiety and depression levels in our population could, therefore, exacerbate the association between sleep disturbance and QoL erroneously.

5.8. Conclusion

In conclusion, most of the patients with FD experience sleep disturbance, with altered sleep quality and insomnia in 81 and 61% of them, respectively. Poor

sleep quality and insomnia are associated with altered QoL, higher severity of symptoms and higher anxiety and depression scores in this disorder. Older age, higher depression scores and severity of dyspeptic symptoms predict the altered sleep quality in FD patients.

5.9. Concluding paragraph

Summary of the main findings

- 18.6% of FD patients displayed normal sleep quality, whereas 81.4% had altered sleep quality.
- 39.4% of FD patients displayed no insomnia whereas 60.6% had insomnia.
- Patients with FD and sleep disturbance:
 - older;
 - decreased QoL;
 - greater severity of their symptoms;
 - higher anxiety and depression scores.
- There was a correlation between sleep quality and QoL in FD patients.
- Independent factors predicting poor sleep quality were:
 - age;
 - depression level;
 - severity of dyspeptic symptoms.

Inferences

- There is a high prevalence of sleep disturbance in patients suffering from FD.
- Sleep impairment comorbidity is associated with lower QoL, higher severity of symptoms and higher anxiety and depression scores in FD.

Perspectives

- Assess objective sleep with polysomnography in FD patients.
- Investigate sleep aids in future clinical trials in FD.

Dissemination

- The data presented in this chapter were published in *Frontiers in Neuroscience* in 2022:

Fabien Wuestenberghs, Chloé Melchior, Charlotte Desprez, Anne-Marie Leroi, Marie Netchitailo, Guillaume Gourcerol. Sleep Quality and Insomnia Are Associated With Quality of Life in Functional Dyspepsia. *Frontiers in Neuroscience* 2022; 16: 829916. <https://doi.org/10.3389/fnins.2022.829916> (IF = 5.15)

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- The content of the manuscript has been presented at the meeting of the European Society of Neurogastroenterology and Motility, NeuroGASTRO 2021, virtual, at the Digestive Disease Week, DDW 2021, virtual, and at the Journées Francophones d'Hépatogastroentérologie et d'Oncologie Digestive, JFHOD 2021, virtual:
 - Fabien Wuestenberghs, Chloé Melchior, Charlotte Desprez, Anne-Marie Leroi, Marie Netchitailo, Guillaume Gourcerol. Sleep quality and insomnia are associated with a lower quality of life in functional dyspepsia [neuroGASTRO 2021 Abstract NGS15372-90]. *Neurogastroenterology & Motility* 2021 ; 33 (S2) : e14244. Special issue: Abstract Supplement for NeuroGASTRO 2021 Congress, September 2-4, 2021 <https://doi.org/10.1111/nmo.14244>
 - Fabien Wuestenberghs, Chloé Melchior, Charlotte Desprez, Anne-Marie Leroi, Marie Netchitailo, Guillaume Gourcerol. Sa391 Sleep disorders are associated with a lower quality of life in functional dyspepsia [DDW 2021 Abstract #Sa391]. *Gastroenterology* 2021 ; 160 (6) : S-488. [https://doi.org/10.1016/S0016-5085\(21\)01873-4](https://doi.org/10.1016/S0016-5085(21)01873-4)
 - Fabien Wuestenberghs, Chloé Melchior, Charlotte Desprez, Anne-Marie Leroi, Marie Netchitailo, Guillaume Gourcerol. La qualité du sommeil et l'insomnie sont associées à la qualité de vie dans la dyspepsie fonctionnelle. *JFHOD* 2021 (Paris, France) [JFHOD 2021 Abstract #000650; communication CO.016]
- Key messages from our work were shared on Twitter 
 - Wuestenberghs, F. [@wuefab] (2022). We showed that #sleep quality and #insomnia were associated with #QualityOfLife in functional #dyspepsia: <https://pubmed.ncbi.nlm.nih.gov/35210990/> @FrontNeurosci #DGBI #FGID #QOL [Twitter] 12 September]. Available on: <https://twitter.com/wuefab/status/1569251104327716864> (Consulted on: September 12, 2022).
 - Wuestenberghs, F. [@wuefab] (2022). Approximately 80% of patients suffering from functional #dyspepsia also have #sleep disturbances based on subjective assessment in tertiary care: <https://www.frontiersin.org/articles/10.3389/fnins.2022.829916/full> @FrontNeurosci @MelchiorChloe @CharlotteDespr3 #DGBI #FGID #SleepQuality [Twitter] 12 September]. Available on: <https://twitter.com/wuefab/status/1569252809861636102> (Consulted on: September 12, 2022).

Impact of the research

- This paper has been cited 1 time [ consulted on March 16, 2023].
- The Altmetric score is 7 [ consulted on March 16, 2023].



Chapter 6 ARTICLE 3. FUNCTIONAL DYSPEPSIA VS CHRONIC NAUSEA AND VOMITING SYNDROME... THE SAME ENTITY OR TWO?

6.1. Introductory paragraph

Articulation with previous projects

Functional dyspepsia and CNVS are disorders defined by symptoms. Criteria used for their definitions are, therefore, of paramount importance. Even if dyspeptic patients frequently report nausea and vomiting, successive Rome criteria have progressively changed the place of those symptoms in FD diagnosis; Rome IV criteria consider nausea as a supportive symptom for FD and merge nausea and vomiting disorders into a single entity termed CNVS. We wanted to question the place of nausea and vomiting symptoms in FD diagnosis: are FD and CNVS different entities or a single disorder?

What is already known?

Dyspeptic patients frequently report nausea and vomiting. Functional dyspepsia and CNVS are separate disorders according to the Rome IV classification.

Research questions

- Is there an overlap between CNVS and FD in a population of investigated dyspepsia?
- Are characteristics of patients with FD+CNVS overlap closer to those of FD patients or CNVS patients?
- Does FD patients suffering from CNVS have a different entity?

Aims

- Assess & compare characteristics and symptoms of patients with FD alone, with CNVS alone and those with coexisting FD and CNVS in a population of investigated dyspepsia.

Chapter 6

Methodology

- Population: 3,471 consecutive patients with investigated dyspepsia at a single tertiary care centre (end 2017 - June 2022)
 - 1,188 patients kept for analysis
 - Functional dyspepsia and CNVS according to Rome IV criteria
- Self-administered questionnaire
 - Quality of life: GIQLI
 - Sleep: PSQI
 - Anxiety and depression: HADS
- Recording of 8 digestive symptoms during the 15 days preceding their appointment
 - frequency assessed prospectively using a 5-point Likert scale

My contribution

I designed the study, I contributed to the analysis and interpretation of the data, I drafted the manuscript and I reviewed critically the manuscript for important intellectual content.

6.2. Title page

Complete title

Frequent overlap between Rome IV chronic nausea and vomiting syndrome and functional dyspepsia among patients with investigated dyspepsia

Short title

Overlap between FD and CNVS

Authors' names

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6.3. Abstract

Background/Aims

Dyspeptic patients frequently report nausea and vomiting. Rome IV distinguishes functional dyspepsia (FD) and chronic nausea and vomiting syndrome (CNVS) as separate disorders. We aimed to assess and compare the characteristics and symptoms of patients with FD alone, CNVS alone and those with FD+CNVS overlap in a population of investigated dyspepsia.

Methods

The retrospective study included 3,471 consecutive patients with investigated dyspepsia. Functional dyspepsia and CNVS were diagnosed according to Rome IV criteria. The severity of dyspeptic symptoms, quality of life, anxiety and depression levels, and comorbidities were assessed.

Key results

Among the 2,317 patients kept for analysis, 651 had FD alone, 144 CNVS alone and 393 FD+CNVS overlap. 73.2% of patients with CNVS fulfil the criteria for FD, whereas 37.6% of FD patients meet the criteria for CNVS. Patients with FD+CNVS overlap had worse quality of life, higher depression levels, and worse sleep quality than both diagnoses alone ($p < 0.05$). All symptoms were at least as prevalent in patients with FD+CNVS overlap as in patients with FD alone, except early satiation.

Conclusions

Nausea and vomiting are frequently reported by patients investigated for dyspepsia. Nearly three-quarters of patients with CNVS fulfil the criteria for FD, whereas more than one-third of FD patients meet the criteria for CNVS. Patients exhibiting FD+CNVS overlap have a more severe disease than those with FD or CNVS alone.

6.4. Introduction

CHRONIC NAUSEA AND VOMITING (CNV) are defined as four weeks or more of nausea and/or vomiting. They are considered of unexplained origin in the absence of an aetiological factor, when the upper GI endoscopy is normal, and if specific conditions (regurgitations, cyclic vomiting and cannabis use) have been excluded (Lacy et al., 2018). Nausea and vomiting disorders impair those patients' HR-QoL (Jung et al., 2019) and have a substantial medico-economic impact (Gourcerol et al., 2022).

Nausea and/or vomiting may be associated with other dyspeptic symptoms (postprandial fullness, early satiation, epigastric pain and/or epigastric burning, bloating, etc.) (Tack et al., 2014, Wuestenberghs et al., 2019). The assessment of uninvestigated dyspepsia makes it possible to identify secondary dyspepsia in some patients, but most have a normal workup and are diagnosed with FD.

Successive Rome criteria have progressively changed the place of nausea and vomiting in FD diagnosis: Rome I included nausea and vomiting in the main criteria for dysmotility-like dyspepsia (Drossman et al., 1994). Rome II kept nausea and recurrent vomiting in the spectrum of dyspepsia (Talley et al., 1999b). Rome III excluded nausea from dyspeptic symptoms, but postprandial nausea could be present in the PDS subtype, while nausea and vomiting disorders were individualised (Tack et al., 2006). Finally, Rome IV criteria considered nausea as a supportive symptom for both PDS and EPS subtypes but indicated vomiting to call into doubt the diagnosis of FD (Stanghellini et al., 2016). Rome IV also merged nausea and vomiting disorders into a single entity termed CNVS, distinguished from CVS and CHS (Aziz et al., 2019a).

Those problems are frequent in the population. A previous study by the Rome Foundation found that FD affects 7.2% of the general population, while CNVS affects 0.9% of the general population (Sperber et al., 2021). The global prevalence of gastroparesis-like symptoms (subjects fulfilling PDS criteria and having nausea and/or vomiting at least once a week) was 0.9% (Huang et al., 2022a).

Our study aimed to assess nausea and vomiting symptoms in a population of investigated dyspepsia by establishing the profile of patients with coexisting FD and CNVS.

6.5. Materials and methods

This study performed a retrospective analysis of prospectively acquired data from Rouen University Hospital, a tertiary centre in France. All patients had given written informed consent before the investigation, in accordance with the revised Declaration of Helsinki (World Medical Association, 2013). The research was registered (ID-RCB number 2017-A02134-49). Approval was obtained from the French data protection authority (Commission Nationale de l'Informatique et des Libertés, CNIL No 817.917) and the research ethics committee (Comité de Protection des Personnes Ile-de-France VII, CPP number 2019/120/OB), in compliance with French legislation.

Patients

Consecutive patients referred for *H. pylori*-negative investigated dyspepsia lasting at least six months (n = 3,471) were investigated from the end of 2017 to June 2022. An organic upper GI disorder was excluded by upper GI endoscopy in all patients.

Exclusion criteria were age under 18 (n = 3), history of significant upper GI surgeries (n = 212, including 67 funduplications and 114 bariatric surgeries), interventions targeting the pylorus such as pyloromyotomy (n = 16), oesophageal motor disorders (n = 29), step III opioid use (n = 30), eating disorders (n = 19), systemic sclerosis (n = 18), diabetes mellitus (n = 251) and with any other organic diseases which could explain the symptoms (n = 62, including patients with Crohn's disease, coeliac disease, large hiatal hernia, autoimmune gastritis or vagal nerve injuries, for example) were not considered for analysis. In addition, patients with CVS (n = 81), CHS (n = 2) and rumination syndrome (n = 20) were not considered, as illustrated in the flow chart (see Figure 6.1).

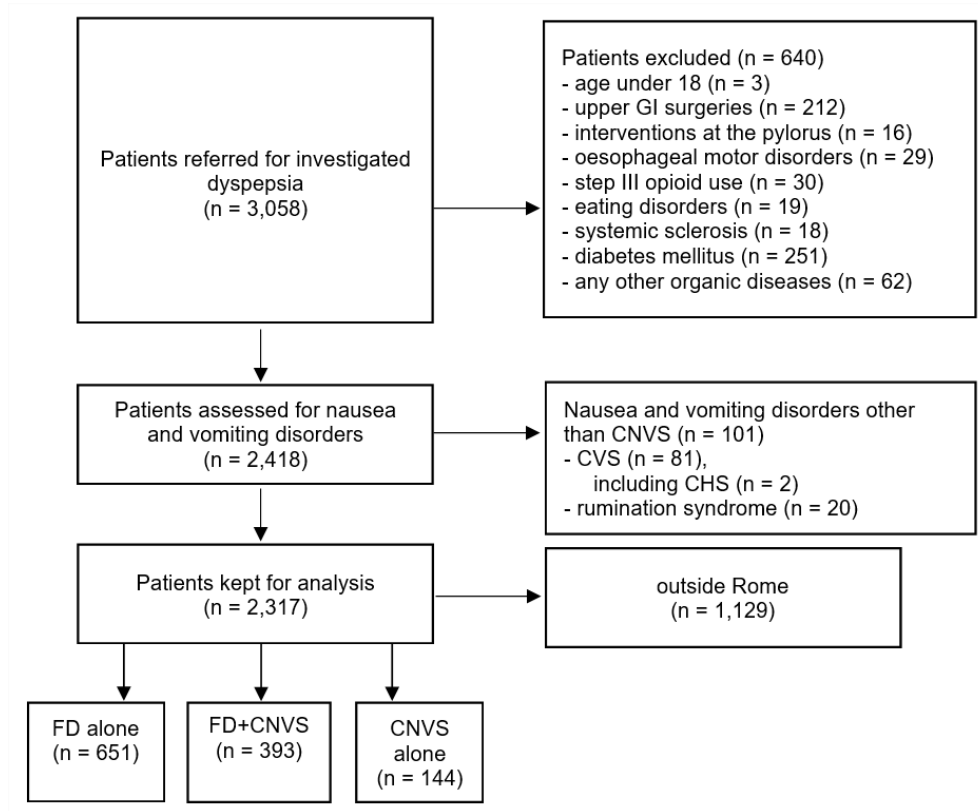


Figure 6.1. Flowchart of patient selection.

CHS: cannabinoid hyperemesis syndrome, CNVS: chronic nausea and vomiting syndrome, CVS: cyclic vomiting syndrome, FD: functional dyspepsia.

Assessment of patients' characteristics

Functional dyspepsia, its subtypes PDS and EPS, IBS and CNVS were defined prospectively according to Rome IV criteria (Stanghellini et al., 2016, Lacy et al., 2016). Patients fulfilling the criteria for FD but with symptoms relieved in all cases by evacuation of faeces or gas were considered not to have FD. Patients with more than 20% of self-induced vomiting were also considered not to have CNVS. Nine digestive symptoms (abdominal pain, belching, bloating, early satiation, epigastric burning, nausea, postprandial fullness, regurgitations, and vomiting) were collected prospectively using a 5-point Likert scale. Symptoms were assessed during the 15 days preceding their appointment and were

graduated from 0 to 4 (0 = absence of the symptom, 4 = extremely severe symptoms).

The GIQLI, a validated score in French (Slim et al., 1999), was used to measure QoL. This score comprises 36 items concerning symptoms, physical state, emotions and social impact. The score ranges from 0 to 144; the higher the score, the better the QoL. Anxiety and depression levels were also assessed using the HADS subscales (Zigmond and Snaith, 1983). Each subscale includes seven items scored from 0 to 3; the higher the score, the higher the anxiety or depression. Sleep was assessed using the PSQI (Buysse et al., 1989). Poor sleep quality was defined by a PSQI greater or equal to five. Patients were asked to report marijuana use and, if applicable, the relief of vomiting after stopping marijuana. Overlaps with self-reported migraine and fibromyalgia were also assessed. Gastric half-emptying time was evaluated in a subgroup of patients by ¹³C-labelled octanoic acid breath testing, as described elsewhere (Wuestenberghs et al., 2019). A subgroup of consecutive patients was asked prospectively to report if vomiting happened to them at least one day per week or less than one day per week.

Study description

Patients kept for analysis were divided into four groups according to Rome criteria: one group fulfilling FD criteria alone (called “FD alone”), one group fulfilling CNVS criteria alone (called “CNVS alone”), one group fulfilling both FD and CNVS criteria (called “FD+CNVS”) and the last group including dyspeptic patients not fulfilling Rome criteria for FD or CNVS (called “outside Rome”). We assessed different characteristics of the patients (age, BMI, QoL, comorbidities, etc.) and the differences between groups in the severity of digestive symptoms during the 15 days before the appointment. Predictors of overlap with CNVS among FD patients were assessed using univariate and multivariate analyses. Analyses of subgroups, with gastric emptying test and/or a specific question for vomiting more or less than once a week available, were performed.

Statistical analysis

Data collection, descriptive statistics and radar plots were performed on spreadsheets using Microsoft® Excel® 2021 MSO 64 bits for Windows® (version 2206, build 16.0.15330.20216, Microsoft® Corporation, Redmond, WA, USA). All the results were expressed by mean and SD. Proportions of patients with different diagnoses were represented in a Venn diagram using the Venn Diagram Plotter software (version 1.6.7458.27187 released on June 02, 2020. PNNL, Richland, WA, United States, <https://pnnl-comp-mass-spec.github.io/Venn-Diagram-Plotter/>). Data were analysed using GraphPad Prism version 9.4.1.681 for Windows® (GraphPad Software Inc., San Diego, CA, USA, www.graphpad.com). The multivariate linear regression analysis was performed using SPSS® software version 27.0.0.0 (IBM® Corp. Released 2020. IBM® SPSS® Statistics for Windows®, Version 27.0. 64 bits edition. Armonk, NY, USA). Quantitative data were compared between groups using the Kruskal-Wallis test (with Dunn's multiple comparisons post-test to compare all pairs of columns if appropriate). In contrast, qualitative variables were compared using the Chi-square test. A multivariate binary logistic regression model with backward Wald stepwise selection (entry probability 0.05 and removal probability 0.10) was used to identify factors associated with overlap with CNVS among all FD patients, using significantly different determinants between FD patients with and without CNVS in univariate analysis, except correlated variables identified by using the variance inflation factor (VIF) with a cut-off of 5 (multicollinearity assessment). Overlap with CNVS was used as the dependent variable, and age, BMI, PDS subgroup, gender, GIQLI, PSQI and HADS-D scores, overlaps with IBS and migraine headaches were used as independent variables. Adjusted OR and their 95% CI were calculated. Two-tailed p-value < 0.05 was considered statistically significant for all analyses.

6.6. Results

Patients' characteristics

Among the 2,317 patients addressed for dyspeptic symptoms and kept for analysis, 1,129 (48.7%) did not fulfil Rome criteria for either FD or CNVS. Among the 1,188 (51.3%) patients with either FD or CNVS diagnosis, 651 (54.8%) had FD

alone, 144 (12.1%) had CNVS alone, and 393 (33.1%) had both FD and CNVS. Therefore, CNVS overlapped with FD in 73.2% of the cases and FD occurred in overlap with CNVS in 37.6% of the cases. The distribution of diagnoses according to Rome criteria in the overall study population is presented in a Venn diagram in Figure 6.2.

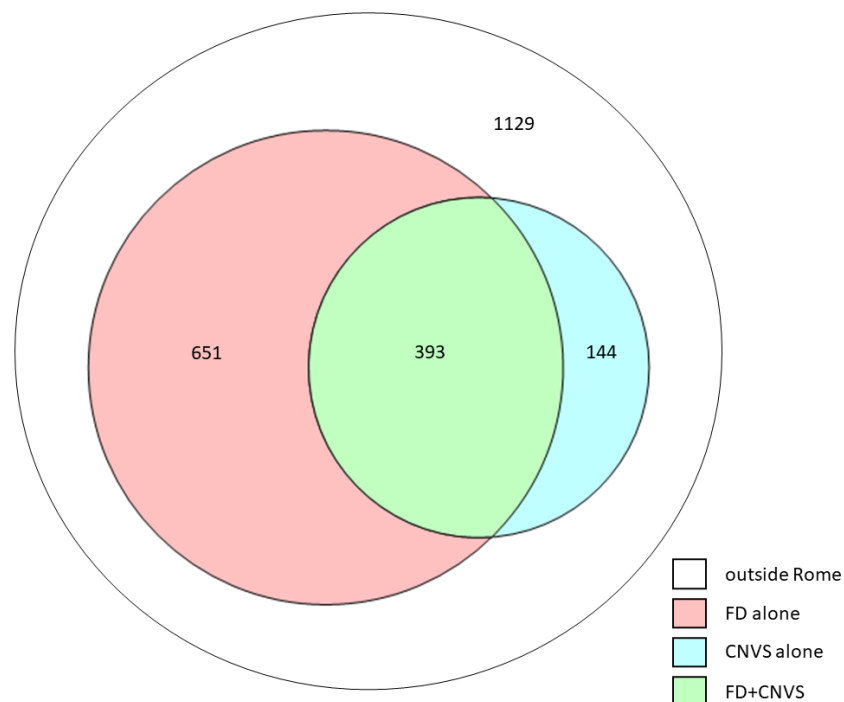


Figure 6.2. Venn diagram summarising the final diagnoses in the study population. Among the 2,317 dyspeptic patients, 1,129 (48.7%) did not fulfil Rome criteria for functional dyspepsia (FD) or chronic nausea and vomiting syndrome (CNVS) and were considered dyspeptic patients “outside Rome”, 651 (28.1%) fulfilled criteria for FD alone, 144 (6.2%) for CNVS alone and 393 (17.0%) for both FD and CNVS (FD+CNVS). The areas of the circles are proportionate to the number of patients.

Comparison of patients’ characteristics according to groups

Overall, all features differed between the four groups with the one-way ANOVA (all p-values < 0.05). All results are shown in Table 6.1.

Patients with FD+CNVS overlap had decreased BMI compared to those with CNVS alone (23.8 ± 5.0 vs 25.3 ± 5.3 kg.m⁻², $p = 0.037$), were more often women than those with FD alone (sex ratio 0.25 vs 0.42, $p = 0.0005$) and reported more frequent marijuana use compared to those with CNVS alone (2.8 vs 0.0%, $p = 0.043$).

Quality of life was lower in patients with FD+CNVS overlap compared to those with either diagnosis alone ($p < 0.0001$ for both). The global HADS score was higher in patients with FD+CNVS overlap compared to those with CNVS alone (17.3 ± 7.2 vs 15.4 ± 7.7 , $p = 0.024$). When analysing HADS subscales, no difference in anxiety levels was found among the three groups with Rome diagnoses. However, depression levels were higher in patients with FD+CNVS overlap compared to those with CNVS alone (7.0 ± 4.2 vs 6.0 ± 4.1 , $p = 0.032$). The proportion of patients with poor sleep quality differed between all groups with Rome diagnoses ($p < 0.05$ for all comparisons), with a lower prevalence in patients with CNVS alone and a higher in those with FD+CNVS overlap. Sleep quality was more impaired in patients with FD+CNVS overlap compared to those with either diagnosis alone based on the results of the PSQI score ($p < 0.05$ for both).

Self-reported migraine headaches were present in 35.8% of all FD patients, whereas self-reported fibromyalgia was reported by 6.8% of them. Patients with FD+CNVS overlap presented more frequently overlap with IBS and migraine headaches than those with FD alone (43.8 vs 37.0%, $p = 0.031$ and 43.0 vs 31.5%, $p = 0.0002$, respectively). However, the prevalence of self-reported fibromyalgia was not different between groups with Rome diagnoses, despite being more prevalent in all those groups compared to the one with patients not fulfilling Rome criteria ($p < 0.0001$).

Table 6.1. Patient characteristics in the overall population and according to Rome diagnoses (outside Rome, FD alone, CNVS alone or FD+CNVS).

	All patients (n = 2,317)	Outside Rome (n = 1,129)	FD alone (n = 651)	CNVS alone (n = 144)	FD+CNVS (n = 393)	p-value
Age, years (mean $\pm$ SD)	47.5 ($\pm$ 15.8)	49.3 ($\pm$ 15.6)	46.8 ($\pm$ 15.4)	46.1 ($\pm$ 16.0)	44.4 ($\pm$ 16.4)	< 0.0001
BMI, kg.m⁻² (mean $\pm$ SD)	24.8 ($\pm$ 5.1)	25.2 ($\pm$ 5.0)	24.6 ($\pm$ 5.2)	25.3 ($\pm$ 5.3)	23.8 ($\pm$ 5.0)	< 0.0001 [§]
Women, n (%)	1,655 (71.4)	776 (68.7)	458 (70.4)	106 (73.6)	315 (80.2)	0.0002 [†]
Cannabis users, n (%)	22 (1.9)	10 (0.9)	11 (1.7)	0 (0.0)	11 (2.8)	0.016 [§]
Overlap with IBS, n (%)	774 (33.4)	308 (27.3)	241 (37.0)	53 (36.8)	172 (43.8)	< 0.0001 [†]
Self-reported migraine, n (%)	717 (30.9)	289 (25.6)	205 (31.5)	54 (37.5)	169 (43.0)	< 0.0001 [†]
Self-reported fibromyalgia, n (%)	115 (5.0)	33 (2.9)	45 (6.9)	11 (7.6)	26 (6.6)	0.0002
GIQLI, mean score ($\pm$ SD)	87.9 ($\pm$ 21.8)	97.1 ($\pm$ 19.3)	82.5 ($\pm$ 19.4)	84.6 ($\pm$ 19.9)	71.2 ($\pm$ 19.9)	< 0.0001 ^{†§}
HADS, mean score ($\pm$ SD)	15.3 ($\pm$ 7.0)	13.4 ($\pm$ 6.7)	16.3 ($\pm$ 6.8)	15.4 ($\pm$ 7.7)	17.3 ($\pm$ 7.2)	< 0.0001 [§]
HADS subscales: HADS-A, mean subscale ($\pm$ SD)	9.4 ($\pm$ 4.2)	8.7 ($\pm$ 4.0)	10.0 ($\pm$ 4.2)	9.4 ($\pm$ 4.5)	10.3 ($\pm$ 4.3)	< 0.0001

Overlap with chronic nausea/vomiting syndrome

HADS-D, mean subscale ($\pm$ SD)	5.9 ($\pm$ 3.9)	5.2 ($\pm$ 3.8)	6.4 ($\pm$ 3.9)	6.0 ($\pm$ 4.1)	7.0 ($\pm$ 4.2)	< 0.0001 [§]
PSQI, mean score ($\pm$ SD)	8.1 ($\pm$ 3.9)	7.2 ($\pm$ 3.5)	8.6 ($\pm$ 3.9)	8.7 ($\pm$ 4.2)	9.7 ($\pm$ 3.8)	< 0.0001 ^{†§}
Poor sleep quality (PSQI $\geq$ 5), n (%)	1,883 (81.3)	839 (74.3)	565 (86.8)	115 (79.9)	364 (92.6)	< 0.0001 ^{††§}

BMI: body mass index, CNVS: chronic nausea and vomiting syndrome, FD: functional dyspepsia, GIQLI: GastroIntestinal Quality of Life Index, HADS: Hospital Anxiety and Depression Scale, HADS-A and HADS-D: HADS Anxiety and Depression subscales respectively, IBS: irritable bowel syndrome, PSQI: Pittsburgh Sleep Quality Index, SD: standard deviation.

The symbols †, ‡, § indicate p-values < 0.05 in FD alone vs CNVS alone, FD+CNVS vs FD alone, and FD+CNVS vs CNVS alone groups, respectively, whereas mentioned p-value concerns the results of the Kruskal-Wallis test or Chi-square analysing outside Rome, FD alone, CNVS alone and FD+CNVS groups together.

Comparison of symptom patterns between the four groups

Among patients with FD (alone or overlapping with CNVS), nausea and vomiting were reported to occur at least “sometimes” in the previous 15 days by 49.6% and 67.6% of the patients, respectively. All symptoms were at least as severe in patients with FD+CNVS overlap as in patients with FD alone, except early satiation. Scores of nausea, vomiting, regurgitations and belching were more severe in groups with CNVS (with or without overlap with FD) than in patients with FD alone. All symptoms were less severe in the group of patients “outside Rome” compared to all other groups, except early satiation. Results are shown in Table 6.2.

Table 6.2. Severity of digestive symptoms during the previous 15 days according to Rome diagnoses (FD alone, CNVS alone, FD+CNVS or dyspeptic patients not fulfilling Rome criteria for FD or CNVS).

	All patients (n = 2,317)	outside Rome (n = 1,129)	FD alone (n = 651)	CNVS alone (n = 144)	FD+CNVS (n = 393)	p-value
Abdominal pain, mean score ($\pm$ SD)	2.08 ($\pm$ 1.16)	1.72 ($\pm$ 1.11)	2.38 ($\pm$ 1.07)	2.04 ($\pm$ 1.15)	2.62 ($\pm$ 1.08)	< 0.0001 ^{†‡§}
Belching, mean score ($\pm$ SD)	1.50 ($\pm$ 1.27)	1.13 ($\pm$ 1.17)	1.65 ($\pm$ 1.27)	1.81 ($\pm$ 1.20)	2.21 ($\pm$ 1.19)	< 0.0001 ^{†§}
Bloating, mean score ($\pm$ SD)	2.40 ($\pm$ 1.14)	2.19 ($\pm$ 1.14)	2.62 ($\pm$ 1.09)	2.44 ($\pm$ 1.10)	2.63 ($\pm$ 1.10)	< 0.0001
Early satiation, mean score ($\pm$ SD)	2.32 ($\pm$ 1.73)	2.57 ($\pm$ 1.67)	2.29 ($\pm$ 1.35)	2.99 ($\pm$ 1.40)	2.10 ($\pm$ 1.35)	< 0.0001 ^{†§}
Nausea, mean score ($\pm$ SD)	1.06 ($\pm$ 1.15)	0.57 ($\pm$ 0.85)	0.87 ($\pm$ 0.94)	2.13 ($\pm$ 0.97)	2.42 ($\pm$ 0.93)	< 0.0001 ^{††}
Postprandial fullness, mean score ($\pm$ SD)	1.94 ($\pm$ 1.23)	1.42 ($\pm$ 1.15)	2.46 ($\pm$ 1.07)	1.78 ($\pm$ 1.05)	2.64 ($\pm$ 1.05)	< 0.0001 ^{†§}
Regurgitations, mean score ($\pm$ SD)	1.25 ($\pm$ 1.18)	0.89 ($\pm$ 1.01)	1.36 ($\pm$ 1.16)	1.62 ($\pm$ 1.23)	1.96 ($\pm$ 1.23)	< 0.0001 ^{†§}
Vomiting, mean score ($\pm$ SD)	2.54 ($\pm$ 1.89)	2.52 ($\pm$ 1.89)	2.53 ($\pm$ 1.88)	2.91 ($\pm$ 1.59)	2.72 ($\pm$ 1.60)	0.18

CNVS: chronic nausea and vomiting syndrome, FD: functional dyspepsia, SD: standard deviation.

The mean scores for individual symptoms are shown, ranging from 0 (absence of symptom) to 4 (most severe).

The symbols †, ‡, § indicate p-values < 0.05 in FD alone vs CNVS alone, FD+CNVS vs FD alone, and FD+CNVS vs CNVS alone groups respectively, whereas mentioned p-value concerns the results of the Kruskal-Wallis test or Chi-square analysing outside Rome, FD alone, CNVS alone and FD+CNVS groups together.

Predictors of overlap with chronic nausea and vomiting syndrome among patients with functional dyspepsia

In univariate analysis, patients with overlapping FD+CNVS were younger (44.4 ± 16.4 vs 46.8 ± 15.4 years old, $p = 0.011$) and leaner (23.8 ± 5.0 vs 24.6 ± 5.2 kg.m-2, $p = 0.026$), displayed more frequently PDS (91.6 vs 77.6% , $p < 0.0001$), were more often women (80.2 vs 70.4% , $p = 0.0005$), had worse QoL (mean GIQLI score of 71.2 ± 19.9 vs 82.5 ± 19.4 , $p < 0.0001$), higher depression scores (mean HADS-D score of 7.0 ± 4.2 vs 6.4 ± 3.9 , $p = 0.024$) and poorer sleep quality (mean PSQI score of 9.7 ± 3.8 vs 8.6 ± 3.9 , $p < 0.0001$), and had more frequently overlaps with IBS (43.8 vs 37.0% , $p = 0.031$) and migraine headaches (43.0 vs 31.5% , $p = 0.0002$) compared to patients with FD alone.

Factors independently associated with CNVS in FD patients were younger age, female gender, more impaired QoL, and PDS subtype. This last criterion explained 10.5% of the variance, while other factors (BMI, PSQI and HADS-D scores, overlaps with IBS and migraine headaches) were not. The model was correct in 66.9% of the cases. The results of the multivariate analysis are shown in Table 6.3.

Table 6.3. Multivariate logistic regression model of factors predicting CNVS overlap among all FD patients according to Rome IV criteria. $R^2 = 0.105$.

	B	SE	OR	95% CI	p-value
Age	-0.012	0.004	0.99	0.98-1.00	0.008
Female gender	-0.32	0.16	0.73	0.53-1.00	0.050
GIQLI score	-0.031	0.004	0.97	0.96-0.98	< 0.0001
HADS-D subscale	-0.036	0.020	0.96	0.93-1.00	0.068
PDS subgroup	-0.91	0.21	0.40	0.27-0.61	< 0.0001
Constant	2.84	0.45	17.1		< 0.0001

B: unstandardised regression coefficient, CI: confidence interval, FD: functional dyspepsia, CNVS: chronic nausea and vomiting syndrome, GIQLI: GastroIntestinal Quality of Life Index, HADS-D: Hospital Anxiety and Depression Scale - Depression subscale, OR: odds ratio, PDS: postprandial distress syndrome, SE: standard error. Factors independently associated with overlapping CNVS among FD patients are indicated in bold.

Assessment of gastric emptying and a cut-off for vomiting in a subset of patients

Gastric half-emptying time was available for 233 patients, among which 104 (44.6%) had FD alone, 22 (9.5%) CNVS alone and 107 (45.9%) FD+CNVS overlap. Mean half-emptying times were not different between groups (161.4 ± 39.7 , 166.1 ± 48.8 and 174.3 ± 139.9 , respectively, $p = 0.35$) or between patients fulfilling Rome criteria for FD compared to those who did not (168.0 ± 103.9 vs 159.5 ± 40.2 , $p = 0.88$).

A subgroup of patients (822 out of the 1,188, 69.2%) were asked prospectively if vomiting happens to them at least one day per week: 108 (13.1%) answered yes and 714 (86.9%) answered no. Gastric emptying was assessed in

173 patients out of 822 (21.0%), among which 69 (39.9%) had delayed gastric emptying. Among those with emptying testing, 22 (48.9%) and 47 (36.7%) had delayed gastric emptying when vomiting happened at least once a week or less than once a week, respectively (OR 1.65 [95% CI: 0.83-3.26], $p = 0.16$). Among the 173 patients assessed for both gastric emptying and cut-off for vomiting, 144 fulfilled criteria for PDS (83.2%). Among those, 55 (38.2%) had delayed gastric emptying and 89 (61.8%) had normal gastric emptying. Among the 616 patients (74.9%) fulfilling PDS criteria, 144 (23.4%) had an emptying test. Among them, 55 (38.2%) had delayed gastric emptying, whereas 89 (61.8%) had normal emptying. Among this subpopulation of PDS patients with both gastric emptying assessment and cut-off for vomiting available, 15 (44.1%) and 40 (36.4%) had delayed gastric emptying when vomiting happened at least once a week or less than once a week, respectively (OR 1.38 [95% CI: 0.66-3.05], $p = 0.43$).

6.7. Discussion

We found that nearly three-quarters of patients with CNVS fulfil the criteria for FD, whereas more than one-third of FD patients meet the criteria for CNVS. Patients with FD+CNVS overlap were more symptomatic for all investigated symptoms (except early satiation) and displayed a higher impact on QoL, depression score and sleep alterations than patients with diagnoses alone.

Our FD population displays similar proportions of subdivision in PDS and EPS than those reported in the literature (Carbone et al., 2015). Female predominance is present, as classically reported in DGBI (Koloski et al., 2002). Persistent vomiting may be associated with another diagnosis than FD and should impose the search for other organic aetiologies. Furthermore, CHS (Soriano-Co et al., 2010) and, more broadly, cannabis use, eating disorders (Murray et al., 2021) and drug-induced nausea and vomiting, could overlap with FD. In our work, opioids and CHS were excluded from analysis, while concomitant cannabis use was only reported by 2% of our population. In addition, all patients from our study underwent an upper GI endoscopy and, when necessary (weight loss or neurological clinical signs, for instance), abdominal and brain imaging. Our study suggests, therefore, that overlap between FD and CNVS exists in the absence of organic causes in tertiary care patients.

Most patients exhibit poor sleep quality and impaired QoL, as shown in FD patients (Wuestenberghs et al., 2022b, Aro et al., 2011). Patients with FD+CNVS overlap have more severe FD symptoms. Worse QoL, higher anxiety-depression scores and increased sleep alterations in the group with overlap between FD and CNVS probably reflect the overlap effect, as reported for other overlaps between DGBI (Aziz et al., 2018b). Similarly, we showed in a previous work that the overlap with IBS and BPS in patients suffering from FD is associated with higher dyspeptic symptoms severity, anxiety, depression, and insomnia levels and reduced QoL and sleep quality (Wuestenberghs et al., 2022a).

Chronic nausea and vomiting pathophysiology is not fully understood (Tornblom and Abrahamsson, 2016). Predictors of the presence of CNVS among FD patients in our work were younger age, being a woman, having more impaired QoL and fulfilling PDS criteria. Chronic nausea and vomiting syndrome and the overlap of FD with CNVS were not associated with delayed GE in our study, as gastric T½ was similar in all groups. Several reports found, however, an association between vomiting and GE in patients with FD or symptoms evocative of gastroparesis, while other reports did not. Moreover, one study showed that patients with nausea and vomiting with normal GE are indistinguishable from those with gastroparesis based on symptom severity, QoL, depression or anxiety scores (Pasricha et al., 2011). Similarly, the presence of vomiting at least once a week was not discriminant for "idiopathic gastroparesis" status among patients fulfilling FD and/or CNVS diagnoses in our cohort. Last, another recent study showed that up to 40% of patients could change their diagnosis over time, passing from FD to gastroparesis and vice versa over one year (Pasricha et al., 2021). Whether delayed GE plays a role in nausea and vomiting associated with FD remains a matter of debate. Autonomic dysfunction was, however, frequently observed in patients with gastroparesis and chronic unexplained nausea and vomiting (Nguyen et al., 2020).

The strengths of our study are that it included a cohort of more than 2,000 patients and that all patients had been investigated by upper GI endoscopy. In contrast, previous work had included fewer patients (Palsson et al., 2016) or uninvestigated patients from the general population (Aziz et al., 2019a). Our limitations include that the study is retrospective, monocentric, and from a tertiary centre. As we did not measure GE in all patients, we cannot rule out that nausea or vomiting could be related to gastroparesis in a subgroup of patients.

The low reporting of cannabis use could be linked to the reluctance of patients to disclose illicit drug use in non-anonymous surveys (Durant et al., 2002).

6.8. Conclusion

In conclusion, our study found that 37.6% of tertiary care patients with FD fulfilled the criteria for CNVS. In comparison, 73.2% of tertiary care patients with CNVS also fulfilled the criteria for FD. Patients with FD+CNVS overlap had more severe dyspeptic symptoms, worse QoL, lower sleep quality, and more overlaps with IBS and migraine headaches than those with FD alone.

6.9. Concluding paragraph

Summary of the main findings

- Nausea and, to a lesser extent, vomiting are frequent among patients consulting for dyspeptic complaints.
- Chronic nausea and vomiting syndrome overlapped with FD in 73.2% of the cases.
- Functional dyspepsia occurred in overlap with CNVS in 37.6% of the cases.
- Patients with FD+CNVS overlap had worse QoL compared to both diagnoses alone.
- All symptoms were at least as prevalent in patients with FD+CNVS overlap as in patients with FD alone.
- The findings are summarised in a graphical abstract (see Addendum 3. Supplementary data for Article 3).

Inferences

- The overlap between FD and CNVS is frequent.
- Patients with overlapping FD and CNVS have the characteristics of FD patients with higher disease severity.

Perspectives

- Investigate if patients fulfilling criteria for both FD and CNVS should be considered as having FD with nausea and/or vomiting, only considering those not fulfilling criteria for FD as having "true" CNVS.
- Questioning the necessity to exclude patients who vomit from the diagnosis of FD in future iterations of the Rome Criteria.

Dissemination

- The data presented in this chapter have been submitted to a peer-reviewed journal.

Impact of the research

- None.



Chapter 7 ARTICLE 4. LINK BETWEEN GASTRIC EMPTYING, SYMPTOM BURDEN, AND QUALITY OF LIFE IN DYSPEPSIA

7.1. Introductory paragraph

Articulation with previous projects

Pathomechanisms involved in FD are incompletely understood. In particular, impaired gastric accommodation, delayed GE and hypersensitivity to gastric distention seem to be involved. Associations between symptoms, QoL and GE in dyspepsia are inconsistent in the literature. As data about GE was available for subgroups of patients in our cohort, we decided to plan a mechanistic study to assess the link between a pathophysiological mechanism and symptoms displayed by patients.

What is already known?

A subgroup of FD patients has delayed GE but the association between GE and dyspeptic symptoms is debated.

Research questions

- Is there an association between symptoms and GE in dyspeptic patients?
- Is there an association between QoL and GE in dyspeptics?

Aims

- Investigate if GE is associated with specific symptoms in dyspeptics.
- Investigate if GE is associated with QoL in dyspeptics.

Methodology

- Retrospective study
- Population: 211 consecutive patients with gastroparesis-like symptoms referred for a GE test at a single tertiary care centre (November 2013 - February 2016)
 - 198 patients kept for analysis
 - Dyspepsia defined outside Rome criteria
 - Patients with diabetes (82.6% were on insulin therapy) and with post-surgical gastroparesis were not excluded since we aimed to

include all dyspeptic patients consulting, and not to focus on idiopathic gastroparesis and FD patients.

- Gastric emptying measured by ^{13}C -labelled octanoate breath testing for more than 6 hours (an example of tracing is shown in Figure 7.1)
- Self-administered questionnaire
 - Gastrointestinal symptoms: 5-point Likert scale & composite score
 - Quality of life: GIQLI

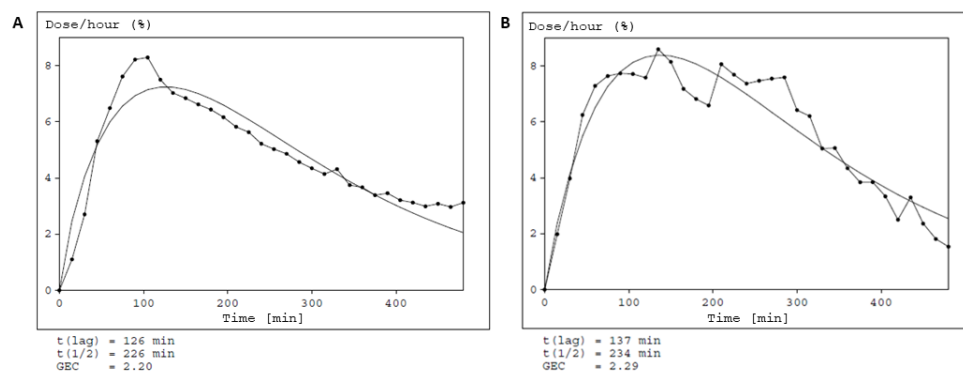


Figure 7.1. Examples of gastric emptying (GE) curves using ^{13}C -labelled octanoate breath testing over 480 minutes in patients with severely delayed GE ($T_{1/2} \geq 200$ minutes).

Cases with a monophasic curve (A) and a biphasic curve^b (B) are shown, with their values of gastric half-emptying time ($T_{1/2}$), gastric lag phase (T_{lag}) and GE coefficient (GEC). Courtesy from Grégory Mosni.

My contribution

I contributed to the analysis and interpretation of the data; I drafted the manuscript, and I revised critically the manuscript for important intellectual content.

^b By arbitrarily defining the peak of excretion as the absence of an increase in the percentage of the given ^{13}C dose excreted per hour for two consecutive measurements and a biphasic curve by the fall of 20% of this dose/hour after the first peak followed by a re-increase of at least 10% of it, 10/47 (21.3%) of the curves were biphasic in the subgroup with the more severely delayed GE ($T_{1/2} \geq 200$ minutes) in our work.

7.2. Title page

Complete title

Association between symptoms, quality of life and gastric emptying in dyspeptic patients

Short title

Gastric emptying & symptoms

Authors' names

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7.3. Abstract

Background/Aims

The association between symptoms, quality of life and gastric emptying in dyspepsia is inconsistent in the literature. Our study investigated if gastric emptying is associated with specific symptoms and quality of life in dyspeptic patients.

Methods

We reviewed retrospectively gastric emptying measured by ^{13}C -labelled octanoate breath testing for more than 6 hours in 198 consecutive patients with dyspepsia complaints. Gastrointestinal symptoms were assessed using a 5-point Likert scale and a symptomatic composite score, whereas the quality of life was measured by the GIQLI.

Key results

In our cohort, 90 patients (45%) had delayed gastric emptying (half-emptying time above 166 minutes when assessed over 6-8 hours). There was no difference in symptoms or quality of life between patients with or without delayed gastric emptying. However, patients with severely delayed gastric (half-emptying time above 200 minutes) had increased postprandial fullness ($p = 0.01$), abdominal pain ($p = 0.03$), bloating ($p = 0.04$), early satiety ($p = 0.02$) and symptomatic composite score ($p = 0.005$) and a lower quality of life ($p = 0.02$). This association was no longer observed if the calculation of gastric emptying was limited to the first 4-hours samples.

Conclusions

There is no association between symptoms, quality of life and gastric emptying in an overall dyspeptic population. However, there is an association between symptoms, quality of life and delayed gastric emptying in the subgroup of patients with severely delayed gastric emptying. An 8-hours measurement of gastric emptying should be recommended.

7.4. Introduction

FUNCTIONAL DYSPEPSIA AND GASTROPARESIS share similar symptoms, including nausea, vomiting, postprandial fullness, early satiety and weight loss. Gastroparesis is defined as a delayed GE without mechanical gastric outlet obstruction (Parkman et al., 2010). Functional dyspepsia is associated with delayed GE in 40 % of the cases (Quartero et al., 1998). Therefore, the distinction between FD and gastroparesis is questioned (Lacy, 2012, Stanghellini and Tack, 2014, Kim and Kuo, 2019).

Methods used in the literature to measure GE time are mostly scintigraphy (Talley et al., 2006a) and breath testing (van Lelyveld et al., 2008). Measurements of GE by scintigraphy or ¹³C-labeled octanoic acid breath testing are known to be well correlated (Choi et al., 1997, Chew et al., 2003). Most of the studies published previously used a measurement over 4 hours since a consensus paper recommends GE scintigraphy to be performed over this period (Abell et al., 2008).

There is no consensus to date in the medical literature about the relationship between symptoms and GE in patients with dyspeptic complaints. Indeed, among 14 studies (Talley et al., 1989, Stanghellini et al., 1996, Talley et al., 2000, Guo et al., 2001, Sarnelli et al., 2003, Talley et al., 2006a, Cassilly et al., 2008, Punkkinen et al., 2008, van Lelyveld et al., 2008, Guo et al., 2012, Ardila-Hani et al., 2013, DiBaise et al., 2016b, Asano et al., 2017a, Tseng et al., 2018) evaluating symptoms and QoL in dyspeptic patients with GE evaluation, only six found a correlation with symptoms (Stanghellini et al., 1996, Guo et al., 2001, Sarnelli et al., 2003, Cassilly et al., 2008, DiBaise et al., 2016b, Tseng et al., 2018). Furthermore, no association with GE delay was observed, even if abdominal pain was correlated to QoL in gastroparesis (Cherian et al., 2010).

Regarding the discrepancy in the literature, our study aimed to investigate whether GE is associated with symptoms and QoL in a cohort of dyspeptic patients, with GE measured by 8-hours ¹³C-labeled octanoic acid breath testing.

7.5. Materials and methods

This monocentric study was performed at the Physiology Unit of Rouen University Hospital in France. This is a retrospective analysis of prospectively

acquired data. All patients had given written informed consent before the investigation, in accordance with the Declaration of Helsinki as revised in 2013 (World Medical Association, 2013). Approval was obtained from the French data protection authority in 2014 (Commission Nationale de l'Informatique et des Libertés, CNIL No 817.917), in compliance with French legislation.

Patients

One hundred and ninety-eight consecutive patients referred for a GE breath test due to dyspeptic symptoms suggestive of gastroparesis lasting for at least six months were investigated from November 2013 to February 2016 in our tertiary care centre. An organic upper GI disorder was excluded by upper GI endoscopy in all patients. Exclusion criteria were age below 18 (n = 2), history of gastric surgery, except fundoplication (n = 9), pregnancy or breastfeeding (n = 0), and patients in whom the breath test was prematurely interrupted before six hours (n = 2). Medications known to alter GE (domperidone, metoclopramide, metopimazine, erythromycin, azithromycin and prucalopride) were asked to be stopped at least one week before the testing.

Evaluation of symptoms and quality of life

Eight dyspeptic symptoms (postprandial fullness, abdominal pain, bloating, regurgitations, nausea, early satiety, belching and vomiting) were collected prospectively using a 5-point Likert scale. These symptoms have been chosen since they are regularly found in the literature (Revicki et al., 2004, DiBaise et al., 2016b). Symptoms were graduated from 0 to 4 during the 15 days preceding the GE measurement, with 4 corresponding to their absence and 0 to extremely severe symptoms. We defined the absence of a symptom by a score greater or equal to 2, and the presence of a symptom by a score inferior to 2 according to the 5-point Likert scale. A TSS was used to evaluate dyspepsia severity and was calculated by adding the eight individual symptoms. The score ranges from 0 to 32; the lower the score, the more severe the symptoms. The GIQLI, a validated score in French (Slim et al., 1999), was used to measure QoL. Anxiety and depression levels were also assessed, using the HADS subscales (Zigmond and Snaith, 1983). Functional dyspepsia and IBS comorbidity were

assessed using Rome III criteria (Longstreth et al., 2006). Post-infectious origin to dyspeptic complaints was evaluated by asking for an episode of gastroenteritis one month before the onset of symptoms (Parkman et al., 2010).

Gastric emptying assessment

Gastric emptying was measured by breath testing in patients starving for 12 hours before the investigation. The technique of carbon 13 (^{13}C)-labelled octanoic acid breath testing, non-invasive and non-ionising, has already been described elsewhere (Ghoos et al., 1993, Gourcerol et al., 2013, Gourcerol et al., 2015). All patients ingested a 250-kcal test meal between 8 and 9 a.m. (Ghoos et al., 1993). The test meal was composed of 19 % of proteins, 43 % of carbohydrates and 38 % of fat, in the form of 50 g of white bread, 17 g of butter and an egg in which 100 μL (91 mg) of ^{13}C -labeled octanoic acid (Euriso-Top, Saint Aubin, France) had been added to mark the solid phase of the test meal. Patients blew in balloons, and exhalations were collected immediately before eating the meal and every 15 minutes after that for up to 8 hours. The presence of ^{13}C -labeled carbon dioxide was detected in breath samplings by infrared spectrometry (Kibion GmbH, Bremen, Germany) (Mion et al., 2001). Gastric half-emptying time was calculated by regression analysis with the equation described by Ghoos *et al.* in 1993 (Ghoos et al., 1993), using the *InfraRed ISotope analyser* software (IRIS; Wagner/Analysen Technik, Bremen, Germany). The equation, expressed as $T_{1/2} = \frac{-1}{k} \ln(1 - 2)^{\frac{-1}{\beta}}$, takes into account the duration of the recording and the percentage of excretion of $^{13}\text{CO}_2$ (Ghoos et al., 1993, Delbende et al., 2000). Gastric emptying was calculated for a single patient on a 4-hour basis, and the study duration (between 6 and 8 hours).

Study description

Gastric half-emptying time, corresponding to the time required for 50% of the ingested meal to leave the stomach, was used to determine GE delay. For the first part of the study, we analysed the results obtained over 6-8 hours using a cutoff for the $T_{1/2}$ of 166 minutes. Indeed, the standard for delayed GE among healthy volunteers was defined by a $T_{1/2} > 166$ minutes for a duration of recording over more than 6 hours in the study of Bromer *et al.* (Bromer et al., 2002). For

study's second part, we arbitrarily defined patients with severely delayed GE as having a $T_{1/2}$ superior to the 75th percentile (200 minutes). Finally, we calculated the $T_{1/2}$ over the first 4 hours of recording to assess the impact of the measurement length on the accuracy of the results.

Statistical analysis

All the results were expressed by mean and SD. Quantitative data were compared using an unpaired t-test, whereas qualitative variables were compared using Fisher's exact test, with 95% CI. The correlation between $T_{1/2}$ and quantitative variables was determined by the Pearson correlation coefficient. Lastly, the accuracy of the GE measurement in relation to the length of the breath test was analysed by a Pearson correlation test, linear regression and a Bland-Altman plot. Data were analysed using GraphPad Prism version 5.03 for Windows (GraphPad Software Inc, San Diego, CA, USA, www.graphpad.com), except for multivariate analysis which was performed using SPSS software version 20.0.0 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp). The univariate and multivariate logistic regression models covariates included age, BMI, diabetes mellitus, gender, GIQLI, heartburn and IBS. Variables significantly associated with $T_{1/2}$ in the univariate analysis were included in the multivariate logistic regression model and then analysed by Forward Wald stepwise selection (entry probability 0.05 and removal probability 0.10), adjusting for the same covariates as used for the univariate model. Two-tailed p-value < 0.05 was considered statistically significant.

7.6. Results

Patient characteristics and their correlation with gastric emptying

Among the 198 analysed patients, 149 (75.3 %) had a complete GE measurement of 8 hours, whereas 49 (24.7 %) had a measurement lasting 6 to 8 hours. There was no difference in QoL in patients with or without diabetes mellitus (GIQLI scores of 78.4 and 80.8, respectively, $p = 0.47$). Patients with IBS presented poorer QoL (GIQLI scores of 71.9 points compared to 83.6 without

overlap with IBS, $p = 0.0024$). The clinical and demographic characteristics of the patients are presented in Table 7.1.

Table 7.1. Patient characteristics.

	Patients (n = 198)
<i>Mean age, years (range)</i>	49.6 (18-83)
<i>Mean BMI, kg.m⁻² (± SD)</i>	25.1 (± 6.1)
<i>Sex ratio Male/Female (% males)</i>	0.55 (35.4)
<i>Mean T½ over 6-8 hours, min (± SD)</i>	187.2 (± 107.2)
<i>Mean T½ calculated over 4 hours, min (± SD)</i>	169.7 (± 78.1)
<i>Diabetes mellitus, n (%)</i>	46 (23.2)
<i>Surgery for GORD or HH, n (%)</i>	25 (12.6)
<i>Fulfilling FD criteria, n (%)</i>	105 (53.0)
<i>Overlap with IBS, n (%)</i>	57 (28.8)
<i>Episode of gastroenteritis before the onset of symptoms, n (%)</i>	9 (4.5)
<i>TSS, mean score (± SD)</i>	16.9 (± 6.3)
<i>GIQLI, mean score (± SD)</i>	80.2 (± 24.6)
<i>HADS, mean score (± SD)</i>	15.7 (± 6.9)
<i>HADS-A, mean subscore (± SD)</i>	9.4 (± 3.9)
<i>HADS-D, mean subscore (± SD)</i>	6.3 (± 4.1)

BMI: body mass index, FD: functional dyspepsia, GORD: gastro-oesophageal reflux disease, GIQLI: GastroIntestinal Quality of Life Index, HADS: Hospital Anxiety and Depression Scale, HADS-A and HADS-D: HADS Anxiety and Depression subscales respectively, HH: hiatal hernia, IBS: irritable bowel syndrome, n = number, SD: standard deviation, T½: gastric half-emptying time, TSS: Total Symptom Score.

No correlation was found between the patient's age ($r = -0.047$; $p = 0.51$) or BMI ($r = 0.062$; $p = 0.39$) and GE. However, GE was correlated with symptom severity assessed by TSS ($r = -0.21$; $p = 0.0024$), QoL assessed by the GIQLI ($r = -0.23$; $p = 0.0013$) and anxiety and depression assessed by HADS ($r = 0.21$; $p = 0.0036$).

Among the overall population, 105 patients (53.0 %) fulfilled Rome III criteria for FD. In the entire FD population, no correlation was found between QoL assessed by the GIQLI and GE ($r = -0.041$; $p = 0.68$). Clinical and demographic characteristics of these patients are presented in Addendum 4. Supplementary data for Article 4 (Supplementary Table 4.1, Supplementary Table 4.2, Supplementary Table 4.3, Supplementary Table 4.6 and Supplementary Table 4.7).

Comparison between patients with a $T_{1/2} \leq 166$ min and > 166 min

One hundred eight patients (54.5 %) had a $T_{1/2} \leq 166$ minutes and 90 patients (45.5 %) had a $T_{1/2} > 166$ minutes. A history of type 1 or type 2 diabetes was more frequent in the group with delayed GE ($p = 0.04$). Other characteristics were similar in both groups and are presented in Table 7.2.

Table 7.2. Characteristics of the population according to gastric half-emptying time ($T_{1/2} \leq 166$ min or > 166 min (measured over 6-8 hours)).

	$T_{1/2} \leq 166$ min (n = 108)	$T_{1/2} > 166$ min (n = 90)	p-value
Mean age, years ($\pm$ SD)	50.0 ($\pm$ 16.1)	49.1 ($\pm$ 14.2)	0.67
Mean BMI, kg.m-2 ($\pm$ SD)	24.4 ($\pm$ 6.0)	25.9 ($\pm$ 6.1)	0.085
Sex ratio Male/Female (% males)	0.54 (35.2)	0.55 (35.6)	1.00

Gastric emptying & symptoms

Diabetes mellitus, n (%)	19 (17.6)	27 (30.0)	0.044*
Surgery for GORD or HH, n (%)	16 (14.8)	9 (10)	0.39
Overlap with IBS, n (%)	32 (29.6)	25 (27.8)	0.87
Episode of gastroenteritis before the onset of symptoms, n (%)	4 (3.7)	5 (5.6)	0.73
TSS, mean score ($\pm$ SD)	17.3 ($\pm$ 6.1)	16.5 ($\pm$ 6.6)	0.39
GIQLI, mean score ($\pm$ SD)	81.2 ($\pm$ 24.3)	79.1 ($\pm$ 24.8)	0.55
HADS, mean score ($\pm$ SD)	15.1 ($\pm$ 6.6)	16.5 ($\pm$ 7.2)	0.14
HADS-A, mean subscore ($\pm$ SD)	9.1 ($\pm$ 3.8)	9.7 ($\pm$ 4.0)	0.24
HADS-D, mean subscore ($\pm$ SD)	6.0 ($\pm$ 4.0)	6.8 ($\pm$ 4.2)	0.17
BMI: body mass index, HH: hiatal hernia, GORD: gastro-oesophageal reflux disease, GIQLI: GastroIntestinal Quality of Life Index, HADS: Hospital Anxiety and Depression Scale, HADS-A and HADS-D: HADS Anxiety and Depression subscales respectively, IBS: irritable bowel syndrome, n = number, SD: standard deviation, TSS: Total Symptom Score. * p < 0.05			

There was no difference between the two groups for all the symptoms, as shown in Table 7.3.

Table 7.3. Symptoms according to gastric half-emptying time ($T_{1/2} \leq 166$ min or > 166 min (measured over 6-8 hours).

	$T_{1/2} \leq 166$ min (n = 108)	$T_{1/2} > 166$ min (n = 90)	p-value
Postprandial fullness, n (mean score)	56 (1.6)	46 (1.5)	1.00
Abdominal pain, n (mean score)	38 (1.9)	39 (1.9)	0.25
Bloating, n (mean score)	50 (1.7)	49 (1.5)	0.32

<i>Regurgitations, n (mean score)</i>	33 (2.3)	31 (2.2)	0.65
<i>Nausea, n (mean score)</i>	26 (2.4)	28 (2.3)	0.34
<i>Early satiety, n (mean score)</i>	44 (2.1)	39 (1.9)	0.77
<i>Belching, n (mean score)</i>	46 (1.9)	38 (1.9)	1.00
<i>Vomiting, n (mean score)</i>	9 (3.4)	10 (3.2)	0.63
<i>TSS, mean score ($\pm$ SD)</i>	17.3 ($\pm$ 6.1)	16.5 ($\pm$ 6.6)	0.39
n = number, TSS: Total Symptom Score.			

Concerning QoL, the GIQLI score was no more correlated to the $T_{1/2}$ ($r = -0.027$; $p = 0.78$) among patients with a $T_{1/2} \leq 166$ minutes, whereas there was a correlation among patients with a $T_{1/2} > 166$ minutes ($r = -0.34$; $p < 0.001$). However, there was no difference in the GIQLI score between the groups with $T_{1/2} \leq 166$ minutes and with $T_{1/2} > 166$ minutes (Table 7.2). Figures are shown in Addendum 4. Supplementary data for Article 4 (Supplementary Figure 4.1).

Comparison between patients with a $T_{1/2} \leq 200$ min and > 200 min

To explain the discrepancy between the correlation of the $T_{1/2}$ with the GIQLI score, whereas the mean GIQLI values were not different in patients with $T_{1/2} \leq$ and $>$ to 166 minutes, we hypothesised that QoL could be linked to the severity of the delayed GE. Characteristics of the population according to the presence or absence of severely delayed GE, using $T_{1/2} > 200$ minutes, corresponding to the 75th percentile, are presented in Table 7.4.

Table 7.4. Characteristics of the population according to gastric half-emptying time ($T_{1/2} \leq 200$ min or > 200 min (measured over 6-8 hours).

	$T_{1/2} \leq 200$ min (n = 151)	$T_{1/2} > 200$ min (n = 47)	p-value
Mean age, years ($\pm$ SD)	49.7 ($\pm$ 16.0)	49.2 ($\pm$ 12.8)	0.82
Mean BMI, kg.m⁻² ($\pm$ SD)	24.8 ($\pm$ 6.2)	25.8 ($\pm$ 5.6)	0.34
Sex ratio Male/Female (% males)	0.56 (35.8)	0.57 (36.2)	0.86
Diabetes mellitus, n (%)	27 (17.9)	19 (40.4)	0.0026*
Surgery for GORD or HH, n (%)	18 (11.9)	7 (14.9)	0.62
Overlap with IBS, n (%)	43 (28.5)	14 (29.8)	0.86
Episode of gastroenteritis before the onset of symptoms, n (%)	6 (4.0)	3 (6.4)	0.45
TSS, mean score ($\pm$ SD)	17.6 ($\pm$ 6.3)	14.7 ($\pm$ 6.0)	0.0049*
GIQLI, mean score ($\pm$ SD)	82.5 ($\pm$ 23.8)	73.0 ($\pm$ 25.5)	0.02*
HADS, mean score ($\pm$ SD)	15.3 ($\pm$ 6.5)	17.2 ($\pm$ 7.8)	0.09
HADS-A, mean subscore ($\pm$ SD)	9.2 ($\pm$ 3.6)	10.1 ($\pm$ 4.6)	0.16
HADS-D, mean subscore ($\pm$ SD)	6.1 ($\pm$ 4.0)	7.1 ($\pm$ 4.3)	0.13
BMI: body mass index, HH: hiatal hernia, GORD: gastro-oesophageal reflux disease, GIQLI: GastroIntestinal Quality of Life Index, HADS: Hospital Anxiety and Depression Scale, HADS-A and HADS-D: HADS Anxiety and Depression subscales respectively, IBS: irritable bowel syndrome, n = number, SD: standard deviation, TSS: Total Symptom Score. * p < 0.05			

There was a significant difference for symptoms of postprandial fullness ($p = 0.012$), abdominal pain ($p = 0.026$), bloating ($p = 0.044$), early satiety ($p = 0.018$) and for the TSS ($p < 0.005$). Results are shown in Table 7.5.

Table 7.5. Symptoms according to gastric half-emptying time ($T_{1/2} \leq 200$ min or > 200 min (measured over 6-8 hours)).

	$T_{1/2} \leq 200$ min (n = 151)	$T_{1/2} > 200$ min (n = 47)	p-value
Postprandial fullness, n (mean score)	70 (1.7)	32 (1.2)	0.012*
Abdominal pain, n (mean score)	52 (2.0)	25 (1.7)	0.026*
Bloating, n (mean score)	69 (1.7)	30 (1.3)	0.044*
Regurgitations, n (mean score)	50 (2.2)	14 (2.3)	0.72
Nausea, n (mean score)	36 (2.5)	18 (2.0)	0.062
Early satiety, n (mean score)	56 (2.1)	27 (1.6)	0.018*
Belching, n (mean score)	61 (2.0)	23 (1.6)	0.32
Vomiting, n (mean score)	14 (3.4)	5 (3.1)	0.78
TSS, mean score ($\pm$ SD)	17.6 ($\pm$ 6.3)	14.7 ($\pm$ 6.0)	0.0049*
n = number, TSS: Total Symptom Score. * $p < 0.05$			

Concerning QoL, the GIQLI score was not correlated to the $T_{1/2}$ among patients with a $T_{1/2} \leq 200$ minutes ($r = 0.035$; $p = 0.67$; Supplementary Figure 4.2A). However, there was a correlation among patients with a $T_{1/2} > 200$ minutes ($r = -0.34$; $p = 0.018$; Supplementary Figure 4.2B). In the group with $T_{1/2} < 200$ minutes, the mean value of the GIQLI score was 82.5 compared to 73.0 in the group with a

$T_{1/2} > 200$ minutes ($p = 0.02$; Supplementary Figure 4.2C). Figures are shown in Addendum 4. Supplementary data for Article 4 (Supplementary Figure 4.2).

In univariate analysis, the only predictor variables of $T_{1/2} > 200$ minutes were diabetes mellitus ($p = 0.005$) and QoL ($p = 0.042$). In multivariate analysis, the only predictor variables of $T_{1/2} > 200$ minutes were also diabetes mellitus ($p = 0.007$) and QoL ($p = 0.044$). Results are shown in Addendum 4. Supplementary data for Article 4 (Supplementary Table 4.4 and Supplementary Table 4.5).

Re-analysis of the data over 4 hours vs > 6 hours

Finally, we compared patients with a $T_{1/2} \leq$ or > 200 minutes after recalculating GE for all the patients with only data from the first 4 hours. We only observed a significant difference in abdominal pain ($p = 0.033$), which was more frequent when $T_{1/2}$ was > 200 minutes, and the TSS, which was slightly decreased when $T_{1/2}$ was > 200 minutes ($p = 0.024$). Other results are shown in Addendum 4. Supplementary data for Article 4 (Supplementary Table 4.8).

The GIQLI score was not correlated to the $T_{1/2}$ for the overall population anymore when using the calculation of $T_{1/2}$ over 4 hours ($r = -0.13$; $p = 0.07$), neither in patients with a $T_{1/2} \leq 200$ minutes ($r = 0.012$; $p = 0.88$) nor in patients with a $T_{1/2} > 200$ minutes ($r = -0.072$; $p = 0.65$). Figures are shown in Addendum 4. Supplementary data for Article 4 (Supplementary Figure 4.3).

We found a strong correlation between the $T_{1/2}$ calculated over the first 4 hours and that established on the entire recording of more than 6 hours for the whole population ($r = 0.70$; $p < 0.0001$; Figure 7.2A). However, a wider dispersion of results was noted for patients with a $T_{1/2} > 200$ minutes after the Bland-Altman analysis (Figure 7.2B). Indeed, the concordance between measures of the $T_{1/2}$ over 4 hours and more than 6 hours was less reliable for a $T_{1/2} > 200$ minutes, considering measurement over 6-8 hours as the gold standard: bias between calculations over 4 hours and more than 6 hours was 14.7 with a SD of 13.3 in patients with a $T_{1/2} \leq 200$ minutes (Figure 7.2C) while bias was 28.1 with a SD of 167.0 in patients with a $T_{1/2} > 200$ minutes (Figure 7.2D).

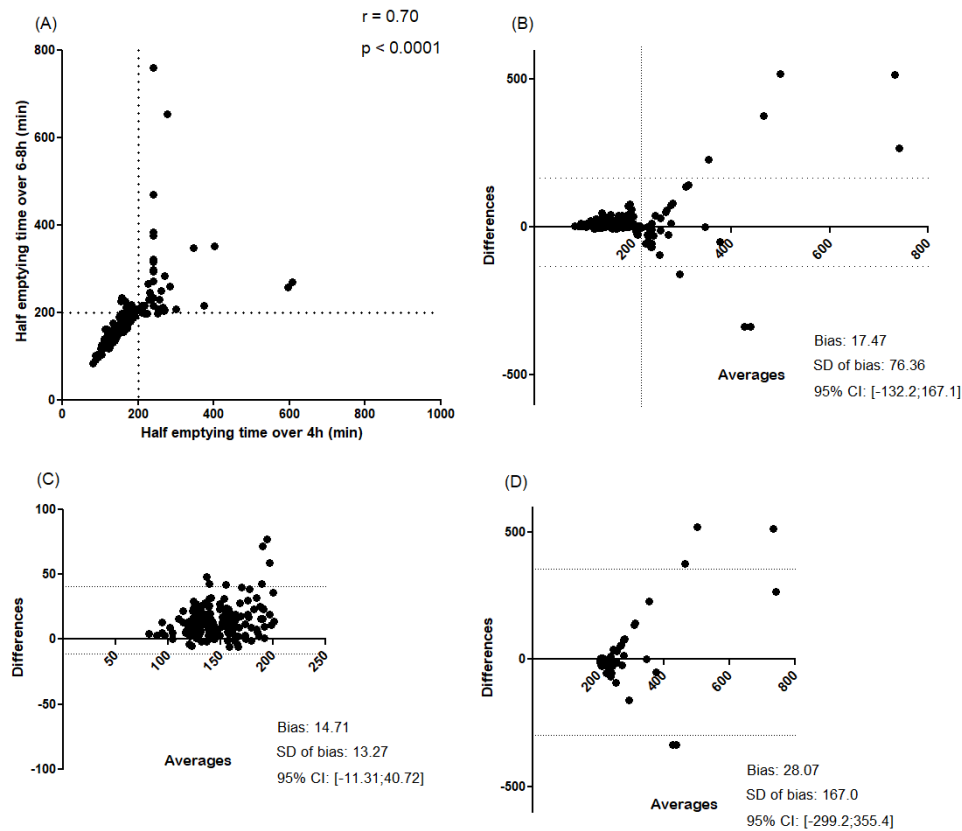


Figure 7.2. Correlation (A) and Bland-Altman plot between the calculations of the gastric half-emptying time ($T_{1/2}$) over 4h and more than 6h for the overall population (B), for a $T_{1/2} \leq 200$ min (C) and for a $T_{1/2} > 200$ min (D).

7.7. Discussion

In the literature, 30 to 40 % of dyspeptic patients present a delayed GE, diagnosed either by scintigraphy (Talley et al., 2006a) or by breath testing (van Lelyveld et al., 2008). We have found 45 % of gastroparesis among dyspeptic patients in our cohort, which is slightly a greater percentage than what is described in the medical literature, maybe because we analysed all dyspeptic patients referred for GE testing, and not only patients with FD according to Rome criteria, but also because of normal values established by Bromer et al. (Bromer et al., 2002).

In our study, GE was broadly correlated to symptom severity, QoL, anxiety, and depression in an unselected population undergoing GE testing. There was no difference in symptoms and QoL between groups with a $T_{1/2} \leq 166$ or > 166 minutes. However, for $T_{1/2} > 200$ minutes, there was a significant difference for postprandial fullness, abdominal pain, bloating, nausea and early satiety, and the TSS score and QoL when the analysis was measured over more than 6 hours. Therefore, our study showed that the link between symptoms and GE exists for patients with severely delayed GE. To be clinically relevant, GE delay thresholds might be based on selecting the more severe patients rather than on statistically abnormal values established among healthy volunteers. The exact norms defining the severity of GE are thus still to be determined, both for a ^{13}C -labeled octanoic acid breath test and for gastric scintigraphy.

Diabetes mellitus was more frequent in groups with delayed or severely delayed GE and predicted the presence of severely delayed GE in multivariate analysis. However, there was no difference in QoL in patients with or without diabetes mellitus in our study. On the contrary, IBS patients presented poorer QoL, but a diagnosis of IBS was not predictive of severely delayed GE in our cohort. Therefore, the alteration of QoL in patients with severely delayed GE is not likely to be explained by diabetes mellitus or IBS, as shown in the supplementary material (see Addendum 4. Supplementary data for Article 4). Since the GIQLI score is a GI-specific QoL questionnaire, it is possible that a more general score like SF-36 could have observed a difference in QoL in patients with or without diabetes mellitus.

Discrepancies in the literature between symptoms and GE could be explained by the heterogeneity of the studies, with different evaluation methods used. Indeed, GE was measured by gastric scintigraphy or ^{13}C -labeled octanoic acid breath testing with various durations of recording, other test meals and non-uniform symptoms collection. Most of the studies published previously used a measurement over 4 hours since a consensus paper recommends GE scintigraphy to be performed over this period (Abell et al., 2008). However, measurements of GE by scintigraphy or ^{13}C -labeled octanoic acid breath testing are well correlated in the literature (Choi et al., 1997, Chew et al., 2003). Indeed, the choice of measurement technique was not implicated in the discrepancy between scintigraphy and breath testing studies showing conflicting results. On the other hand, most of the studies published previously used a measurement over 4 hours

(Abell et al., 2008). Our work suggests that the discrepancy found in the literature could, partially, be linked to the duration of the measurement of GE. Indeed, differences among symptoms were correlated to the $T_{1/2}$ calculated over more than 6 hours but not if the calculation was limited to 4 hours in our study. This is probably due to a lack of measurement accuracy if limited to 4 hours once the $T_{1/2}$ exceeds 200 minutes. Measuring GE with ^{13}C -labeled octanoic acid breath testing over 6 hours is more reliable than over 4 hours (Clegg and Shafat, 2010). This has been confirmed in our study by a Bland-Altman analysis. The variability between measures over 4 hours and more than 6 hours was three times superior when the $T_{1/2}$ threshold was set at 200 minutes compared to 166 minutes. A better estimation of the real emptying time could be the explanation of the correlation found only in 8-hour measurements. Furthermore, our protocol could theoretically better select patients in whom accelerating GE could be a better target for symptom improvement. All these elements favour a measurement of GE over 8 hours in current practice when using ^{13}C -labeled octanoic acid breath testing. Similar results were found by Choi *et al.* (Choi et al., 1998), with better correlation when using breath testing compared to gastric scintigraphy for measurements over 6 hours rather than 4 hours. However, implementing an 8-hours measurement in daily practice is patient-unfriendly and increases the cost of the procedure. Future studies should focus on identifying new algorithms to extrapolate the correct $T_{1/2}$ from shorter measurements.

Another possible explanation for the discrepancy relies on the test meal. The study of Bromer *et al.* (Bromer et al., 2002), from which the norm of 166 minutes comes, used a muffin of 350-kcal (Perri et al., 2010) in which 100 mg of ^{13}C -labeled octanoic acid was added. Our choice to use a different test meal from the one used in the study of Bromer *et al.* (Bromer et al., 2002) is justified because it is a test-meal similar to the one used in the study by Ghooos *et al.* (Ghooos et al., 1993) from which our equation is based and because it is the most widely used in investigations, even if these are limited to 4-hours measurements (Sarnelli et al., 2003, Arts et al., 2007). Moreover, a high caloric load leads to poor tolerance in many dyspeptic patients since it is known to delay GE (Marciani et al., 2001). In our study, during the inclusion period, some patients vomited their test meal, which was only 250 kcal.

On the other hand, the study of Bromer *et al.* (Bromer et al., 2002) defined delayed GE as a $T_{1/2} > 166$ minutes if the measurement was done over

more than 6 hours. This norm was established upon only nine healthy volunteers. This value necessitated to be reevaluated by complementary studies since it could overestimate the number of patients defined as suffering from gastroparesis. This could explain in part the fact that we did not find any difference for symptoms or QoL between groups. In our study, the definition of the more severe patients was defined arbitrarily to the 75th percentile.

Our work has several limitations. First, a monocentric study realised in a tertiary hospital implies that patients could have a more severe disorder compared to those in secondary care. Nevertheless, most available studies in the literature have been realised in tertiary referral centres, and this only factor cannot be incriminated to explain discrepancies between studies. Symptoms were collected prospectively, permitting to avoid biases due to heterogeneous measurements. Patients from whom we could not calculate the T½ have not been retained in the study. In the study, there was no significant difference concerning vomiting. Since some patients had vomited their test meal, their exclusion could have led to a selection bias since excluding the more severe patients imply not reflecting the dyspeptic population of origin anymore (Parkman et al., 2016). However, the number of those patients is minimal (4 patients, 2 %). Finally, we did not realise any subgroup analysis according to treatments, especially as patients had to stop every treatment that could interact with the measurement of GE before the test.

Delayed GE could not explain all the different symptomatic profiles. Indeed, some studies have found other pathophysiological mechanisms like visceral hypersensitivity or gastric compliance disorders as triggers of dyspeptic symptoms (Bisschops et al., 2008, Kumar et al., 2008). It is unlikely that GE itself could be the origin of all symptoms in gastroparesis. This is suggested in part by therapeutic trials. Indeed, the efficacy of gastric electrical stimulation on refractory nausea and vomiting is not linked to the acceleration in GE (Gourcerol et al., 2007). Furthermore, the use of prokinetics (Talley et al., 2000, Talley et al., 2001a, Sugumar et al., 2008, Janssen et al., 2013, Tack et al., 2016b) or injections of intra-pyloric botulinum toxin (Arts et al., 2007, Friedenberg et al., 2008) did not improve symptoms in comparison to the placebo, despite accelerating GE. Another study evaluating the efficacy of relamorelin, a selective ghrelin receptor (GSH-R) agonist, accelerates GE in diabetic patients and reduces the frequency and severity of vomiting compared to a placebo (Lembo et al., 2016). However,

the authors emphasised that there was no correlation between the acceleration of the GE and the improvement of symptoms. Up to now, there are only scarce data regarding the correlation between GE acceleration and symptom improvement in gastroparesis (Malik et al., 2018).

When performing subgroup analysis with all FD patients, we did not find any association between QoL and T½. Showing an impact of the severity of GE delay in the overall dyspeptic population and not in FD patients suggests that the population of FD patients is too small to show a difference in our study. Therefore, these results suggest looking at the impact of severely delayed GE on symptoms and QoL in a larger cohort of FD patients.

7.8. Conclusion

In conclusion, our study demonstrates no association between symptoms, QoL and GE measured with breath testing in an overall dyspeptic population. However, in patients with severely delayed GE, GE is associated with symptoms and QoL, but this requires an 8-hours measurement. Indeed, a severely delayed GE can be diagnosed accurately only with an 8-hours measurement during ¹³C-labeled octanoic acid breath testing.

7.9. Concluding paragraph

Summary of the main findings

- 45% of the patients had a delayed GE ($T_{1/2}$ above 166 minutes when assessed over 6-8 hours).
- No difference in symptoms or QoL between patients with or without delayed GE.
- Patients with severely delayed gastric ($T_{1/2}$ above 200 minutes, corresponding to the percentile 75 in our cohort as shown in Figure 7.3) had increased postprandial fullness, early satiation, abdominal pain, bloating, and a lower QoL.
- The association with symptoms and QoL was no longer observed if the calculation of GE was limited to the first 4-hours samples.

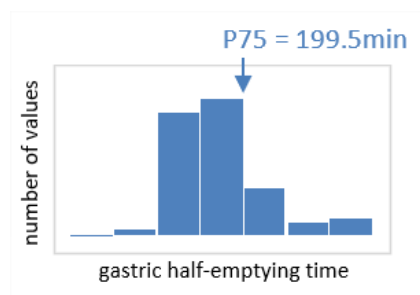


Figure 7.3. Distribution of the gastric half-emptying times among our cohort, with the percentile 75 (P75) corresponding to 199.5 minutes.

Inferences

- There is no association between symptoms, QoL and GE in an overall dyspeptic population.
- There is an association between symptoms, QoL and delayed GE in the subgroup of patients with severely delayed GE.
- An 8-hour measurement of GE should be recommended when using ^{13}C -labelled octanoate breath testing.

Perspectives

- Replicate our results in a cohort assessed by gastric scintigraphy.

Chapter 7

- Assess the link between upper GI symptoms in FD and other physiological parameters (pyloric distensibility, etc.).
- Perform a meta-analysis of studies evaluating the link between GE and digestive complaints of FD patients.

Dissemination

- The data presented in this chapter have been published in the *Journal of Neurogastroenterology and Motility* in 2019.

Fabien Wuestenberghs, Mathilde Juge, Chloé Melchior, Charlotte Desprez, Anne-Marie Leroi, Guillaume Gourcerol. Association between symptoms, quality of life and gastric emptying in dyspeptic patients. *Journal of Neurogastroenterology and Motility* 2019 Oct 30; 25 (4): 534-543. <https://doi.org/10.5056/jnm19060> (IF = 3.01)

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- Our work was highlighted by an editorial in the issue in which it was published (Lee, 2019).
- Key messages from our work were shared on Twitter :
 - Wuestenberghs, F. [@wuefab] (2019). My first original research article has been published in @JNMjournal and assesses the association between symptoms, quality of life and gastric emptying in dyspeptic patients. <http://jnmjournal.org/journal/view.html?doi=10.5056/jnm19060> #dyspepsia [Twitter] 9 October]. Available on: <https://twitter.com/wuefab/status/1182029782315343873> (Consulted on: September 12, 2022).
 - Wuestenberghs, F. [@wuefab] (2019). We found an association between symptoms, quality of life and delayed gastric emptying in the subgroup of patients with severely delayed gastric emptying. <http://jnmjournal.org/journal/view.html?doi=10.5056/jnm19060> #dyspepsia [Twitter] 9 October]. Available on: <https://twitter.com/wuefab/status/1182029998930190337> (Consulted on: September 12, 2022).

Impact of the research

- This paper has been cited 17 times [ consulted on March 16, 2023].
- The Altmetric score is 1 [ consulted on March 16, 2023].



Chapter 8 ARTICLE 5. ASSESSMENT OF OVERLAPS WITH BLADDER PAIN SYNDROME AND IRRITABLE BOWEL SYNDROME IN FUNCTIONAL DYSPEPSIA

8.1. Introductory paragraph

Articulation with previous projects

We found in our systematic review that overlaps associated with FD are not limited to digestive disorders but can also involve extra-digestive ones. The colon, stomach and bladder are the three main abdominal organs shared by both genders in humans. The interplay between the bladder and the colon is well described. Functional dyspepsia and BPS are also both well-known to overlap with IBS. However, whether FD overlaps with BPS remained unknown.

What is already known?

Overlaps with IBS and/or OAB occur in a subgroup of FD patients. Patients with overlapping FD-IBS have higher disease severity, lower QoL, higher anxiety and depression levels, and more sleep disturbance.

Research questions

- What is the prevalence of BPS in FD?
- What is the impact of overlapping BPS and/or IBS in patients with FD?

Aims

- Assess the presence of BPS in patients with FD.
- Assess the impact of the overlap with BPS in patients with FD.

Methodology

- Population: 1,650 consecutive patients with investigated dyspeptic symptoms at a single tertiary care centre (March 2015 - November 2018)
 - 1,453 patients kept for analysis
 - 892 patients suffering from FD

- Definitions:
 - Functional dyspepsia and IBS: according to Rome III & IV criteria
 - Bladder pain syndrome: according to ESSIC criteria (see Table 8.1)
- Self-administered questionnaire
 - Quality of life: GIQLI
 - Sleep: PSQI and ISI
 - Anxiety and depression: HADS
 - Dyspeptic symptom severity: individual questions for eight dyspeptic complaints

Table 8.1. ESSIC criteria for bladder pain syndrome.

Pelvic pain	Chronic (≥ 6 months)	Persistent urge to void
Pelvic pressure		Permanent urge to void
Pelvic discomfort		Urinary frequency $> 8/d$
		Nycturia

My contribution

I designed the study, contributed to the analysis and interpretation of the data, drafted the manuscript, and revised the manuscript critically for important intellectual content.

8.2. Title page

Title

Overlaps with bladder pain syndrome and irritable bowel syndrome are associated with higher symptom burden and reduced quality of life in functional dyspepsia

Short title

IBS & BPS overlaps in functional dyspepsia

Authors' names

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8.3. Abstract

Background/Aims

Functional dyspepsia and bladder pain syndrome are well-known to overlap with irritable bowel syndrome. Whether functional dyspepsia overlaps with bladder pain syndrome remains unknown. Our aim was to evaluate the presence of bladder pain syndrome in functional dyspepsia patients and its impact.

Methods

All consecutive patients with investigated dyspeptic symptoms in our tertiary care centre between March 2015 and November 2018 were studied. Functional dyspepsia and irritable bowel syndrome were diagnosed according to Rome III and IV criteria, while bladder pain syndrome was diagnosed using ESSIC criteria. Validated questionnaires were filled to assess the quality of life (GIQLI), anxiety and depression (HADS), sleep (PSQI) and insomnia (ISI). Dyspeptic symptom severity was assessed individually for eight dyspeptic complaints.

Key results

Among 1,453 patients with dyspeptic symptoms, 61.4% fulfilled Rome criteria for functional dyspepsia. Bladder pain syndrome was present in 16.0% of the patients not fulfilling diagnostic criteria for functional dyspepsia, 22.2% of patients with functional dyspepsia alone and 36.4% of patients with overlapping functional dyspepsia and irritable bowel syndrome ($p < 0.0001$). In patients with bladder pain syndrome overlapping with functional dyspepsia, dyspeptic symptom severity, anxiety, depression, and insomnia levels were higher, while the quality of life and sleep quality were reduced ($p < 0.0001$). These results were even more pronounced in case of overlap with irritable bowel syndrome ($p < 0.0001$).

Conclusions

Bladder pain syndrome is present in 26.9% of functional dyspepsia patients and is associated with higher gastrointestinal and psychological distresses, and sleep symptom burdens, and with reduced quality of life.

8.4. Introduction

OVERLAP BETWEEN FGIDS, NOW CALLED DGBI, is frequent (de Bortoli et al., 2018). Functional dyspepsia and IBS are well known to overlap, both conditions being more prevalent in patients with the other one compared to the general population, which indicates an association between them (Agréus et al., 1995, Whitehead et al., 2002). Overlapping FD-IBS is associated with altered QoL (Aro et al., 2011) and impaired sleep (Kim et al., 2018b), and those patients experience more severe GI symptoms (von Wulffen et al., 2019), have higher depression levels (Choi et al., 2017) and higher somatic symptom scores (Van Oudenhove et al., 2011c). Similar results have been reported for the overlap with GORD (Fujiwara et al., 2011).

Bladder pain syndrome and overactive bladder (OAB) are the main functional bladder disorders (Leue et al., 2017). BPS is characterised by pelvic pain associated with lower urinary symptoms. BPS had successive definitions, including interstitial cystitis and IC/painful bladder syndrome (Meijlink, 2014). Bladder pain syndrome is currently diagnosed using the ESSIC criteria (van de Merwe et al., 2008). Overactive bladder is characterised by urinary urgency, with or without incontinence, in the absence of painful symptoms (Drake, 2014). Overactive bladder and BPS remain, therefore, different entities that may coexist (Regauer et al., 2017, Ackerman et al., 2019).

Functional dyspepsia and BPS are both prevalent in the general population: 7.2% and 3.7%, respectively (Ibrahim et al., 2007, Sperber et al., 2021). Overactive bladder is common in FD patients, with a frequency of 20.5% in the disorder (Matsuzaki et al., 2012). Likewise, dyspeptic symptoms are known to be a frequent complaint in patients with BPS (Chelimsky et al., 2012). However, the impact of the overlap with BPS and FD has never been assessed, neither on QoL, symptom severity, nor other characteristics in FD patients. Therefore, our study aims to determine the prevalence of BPS in FD and FD-IBS patients and the symptom burden in these populations, including dyspeptic symptom severity, QoL, anxiety, depression, sleep quality and insomnia.

8.5. Materials and methods

This study is based on a retrospective analysis of prospectively acquired data from Rouen University Hospital. All patients had given written informed consent for data to be recorded and used for research, in accordance with the Declaration of Helsinki as revised in 2013 (World Medical Association, 2013). Approval was obtained from the French data protection authority (Commission Nationale de l'Informatique et des Libertés, CNIL No 817.917), in compliance with French legislation. Ethical approval for the analysis of the data was obtained (CERNI No E2019-38).

Patients

We analysed retrospectively all patients referred between March 2015 and November 2018 at our centre for chronic dyspeptic symptoms. All patients had normal endoscopies without *H. pylori* on the biopsies and normal routine blood tests. Patients who incompletely filled out the Rome questionnaire, patients with diabetes, patients aged under 18 and patients with rumination, cyclic vomiting and cannabinoid hyperemesis syndromes were excluded.

Diagnostic criteria

Functional dyspepsia, its subtypes PDS and EPS, and IBS were defined according to Rome III criteria (Tack et al., 2006, Longstreth et al., 2006) between March 2015 and the end of 2017, and according to Rome IV criteria (Stanghellini et al., 2016, Lacy et al., 2016) between the end of 2017 and November 2018. A post-infectious origin to dyspeptic complaints was evaluated by asking for an history of acute gastroenteritis during the month preceding the onset of dyspeptic symptoms (Parkman et al., 2010).

Bladder pain syndrome was defined using an 8-item symptom-based self-questionnaire based on the ESSIC criteria published in 2008 (van de Merwe et al., 2008) (see Supplementary Table 5.1 in Addendum 5. Supplementary data for Article 5). All patients should have at least three criteria to be diagnosed with BPS: (1) pain, pressure or discomfort perceived to be related to the urinary bladder, (2) symptoms of at least six months, and (3) persistent or intermittent urge to void,

pollakiuria (superior to eight mictions per day) or nycturia (at least one miction per night).

Symptom questionnaires

The GIQLI, a validated score in French (Slim et al., 1999), was used to measure QoL. This score is composed of 36 items concerning symptoms, physical state, emotions, and social impact. The score ranges from 0 to 144; the higher is the score, the better is the QoL.

Anxiety and depression levels were assessed, using the HADS and its subscales (HADS-A and HADS-D, respectively) (Zigmond and Snaith, 1983). Each subscale includes seven items scored from 0 to 3; the higher the score, the higher the anxiety or depression.

Sleep quality was assessed using the PSQI (Buysse et al., 1989). The level of insomnia was defined by the ISI questionnaire (Bastien et al., 2001).

Eight individual symptoms (postprandial fullness, abdominal pain, bloating, regurgitations, nausea, early satiety, belching and vomiting) were assessed using individual questions from the GIQLI for all of them except vomiting. Symptoms were graded from 0 to 4 during the 15 days preceding their appointment, with 0 corresponding to their absence and 4 to extremely severe symptoms. We defined two groups for each symptom: “absence of symptom” by a score lower or equal to 2, and “presence of symptom” by a score higher than 2 according to the 5-point Likert scale.

Gastric emptying

Gastric emptying time was assessed in a subgroup of patients by ¹³C-labelled octanoic acid breath testing as described elsewhere (Wuestenberghs et al., 2019). Briefly, patients ingested a 250-kcal test meal containing ¹³C-labeled octanoic acid (Euriso-Top, Saint Aubin, France), with exhalations of air being collected before and every 15 minutes after the meal for 6-8 hours. The presence of ¹³C-labeled CO₂ was detected by infrared spectrometry (Kibion GmbH, Bremen, Germany) and T½ could therefore be calculated using the software *InfraRed ISotope analyser* (IRIS; Wagner/Analysen Technik, Bremen, Germany) (Ghoos et

al., 1993). Delayed GE was defined as a $T_{1/2}$ superior to 166 minutes according to Bromer et al. (Bromer et al., 2002)

Study design

Consecutive patients with dyspeptic symptoms were screened for FD, IBS and BPS. Patients were divided into five groups according to the presence and/or combination of FD, IBS and BPS diagnostic criteria: “symptomatic controls” if no diagnostic criterium was present, FD alone, FD-IBS, FD-BPS or FD-IBS-BPS. Our “symptomatic controls” are, therefore, composed of patients referred for dyspeptic symptoms who did not fulfil Rome criteria for FD, but also for IBS and BPS. Characteristics of the patients, QoL, anxiety, depression, sleep quality and insomnia were compared between diagnostic groups.

A comparison of Rome III and IV cohorts was performed for quality control (see Supplementary Figure 5.3, Supplementary Figure 5.4 and Supplementary Figure 5.5 in Addendum 5. Supplementary data for Article 5).

Statistical analysis

All results were expressed as mean $\pm$ SD. Quantitative data between groups of patients were compared using a non-gaussian unpaired t-test (Mann-Whitney test), whereas qualitative variables were compared using Fisher’s exact test, both with 95% CI. Multiple groups comparisons were performed using Kruskal-Wallis test with Dunn's multiple comparison post-test to compare all pairs of columns, with a significance level alpha of 0.05%. A multiple linear regression model was fitted to identify predictors of overlapping BPS in our cohort of FD patients using the following independent variables: age, BMI, gender, GIQLI score, HADS, presence of IBS, and PSQI score. Multicollinearity was detected using the variance inflation factor, and correlated variables were removed from the regression model. Two-tailed p-value < 0.05 was considered statistically significant. The principal component analysis (PCA) factors were age, BMI, GIQLI, the eight dyspeptic symptoms individually, HADS-A and HADS-D subscales, and PSQI. We used all dimensions with eigenvalues superior to 1 to select principal components for analysis.

Data relied on spreadsheets using Microsoft® Excel® for Office® 365 version 1910 for Windows® (build 16.0.12130.20382, Microsoft Corporation®, Redmond, WA, USA) and were analysed using GraphPad® Prism® version 5.03 for Windows® (GraphPad Software, Inc.®, San Diego, CA, USA, www.graphpad.com), except descriptive statistics which were performed with Microsoft® Excel®, univariate and multivariate analyses which were performed using SPSS® software version 27.0.0.0 (IBM® Corp. Released 2020. IBM® SPSS® Statistics for Windows®, Version 27.0. Armonk, NY, USA: IBM Corp) and mediation analysis and PCA which were performed using RStudio® software version 1.2.1335 (RStudio® Team (2016). RStudio: Integrated Development for R. RStudio, Inc.®, Boston, MA, USA, www.rstudio.com), based on R software version 3.6.1 (R Core Team (2019). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. <https://www.R-project.org/>), the psych package version 1.8.12 (Revelle, 2018) and the FactoMineR package version 1.34 (Lê et al., 2008).

Venn diagrams were used to represent the proportions of subjects with different diagnoses using the Venn Diagram Plotter software (version 1.5.5228.29250 released April 25, 2014. PNNL, Richland, WA, USA, <http://omics.pnl.gov/>).

Other analyses included investigation of factors associated with overlap with BPS using univariate and multivariate analyses, PCA, GE study in a subgroup of patients, and comparison of Rome III and IV cohorts.

8.6. Results

Patient characteristics

One thousand six hundred and fifty-five patients addressed for dyspeptic symptoms were identified in the eligible period. Patients who incompletely filled out the Rome questionnaire (n = 6), patients with diabetes (n = 160), patients aged under 18 (n = 8) and patients with rumination, cyclic vomiting and cannabinoid hyperemesis syndromes (n = 28) were not considered for further analysis. A total of 1453 patients were kept for analysis. Among them, 892 (61.4%) patients fulfilled criteria for FD, classified as PDS in 58.7%, EPS in 14.9%, and PDS-EPS in 26.4%; among them, 465 (52.1%) patients had FD-alone, 187 (21.0%)

patients had FD-IBS, 133 (14.9%) patients had FD-BPS and 107 (12.0%) patients had FD-IBS-BPS overlaps (Figure 8.1). Clinical and demographic characteristics of the overall population and “symptomatic controls” are presented in Table 8.2. Principal component analysis was used to visualise graphically our data and assess the relationship between variables (Supplementary Figure 5.1, Supplementary Figure 5.2, and Supplementary Table 5.2 in Addendum 5. Supplementary data for Article 5).

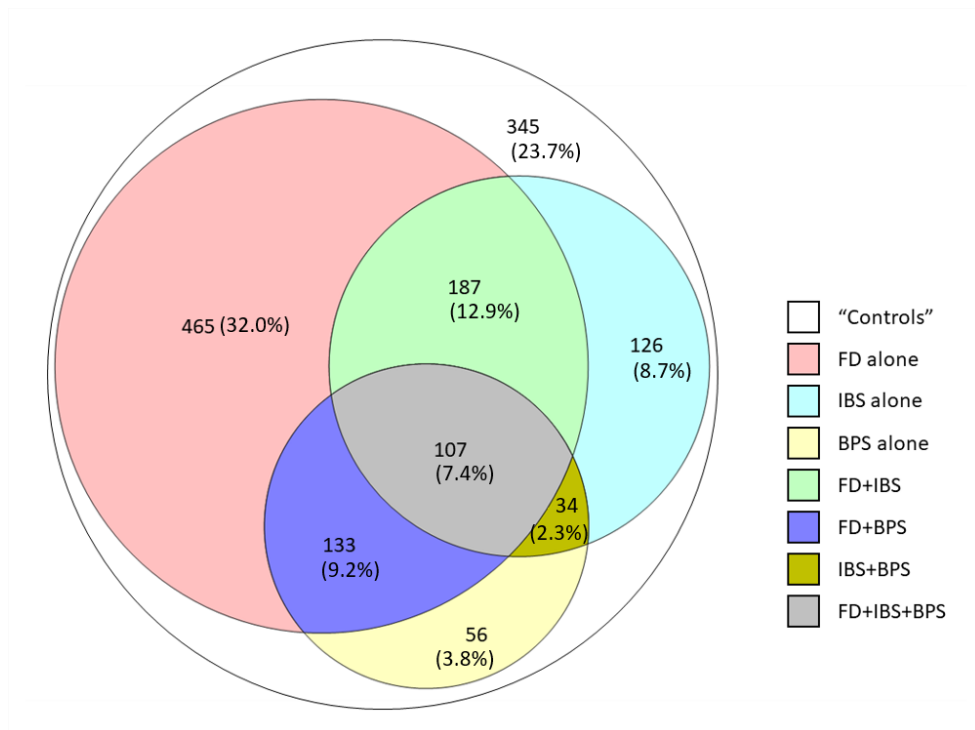


Figure 8.1. Venn diagram of the study population.

Venn diagram summarising overlap syndromes. The numbers of subjects within each diagnostic group are shown, with areas of the circles being proportionate to the number of patients. “Controls” stands for “symptomatic controls” in the legend.

BPS: bladder pain syndrome, FD: functional dyspepsia, IBS: irritable bowel syndrome.

Table 8.2. Patients' characteristics in the overall dyspeptic population, in "symptomatic controls", and in the different groups.

	Overall population (n = 1,453)	"Sympt- omatic controls" (n = 345)	FD alone (n = 465)	FD-IBS (n = 187)	FD-BPS (n = 133)	FD-IBS- BPS (n = 107)	p-value
Mean age, years	47.4 (± 15.7)	49.3 (± 16.1)	48.1 (± 15.5)	44.8 (± 15.7) *	48.8 (± 15.4)	43.7 (± 13.9) *	0.0016
Mean BMI[§], kg.m⁻²	24.7 (± 5.3)	25.4 (± 4.9)	24.6 (± 5.5)*	24.7 (± 5.5)	23.8 (± 4.4)*	24.3 (± 5.4)	0.011
Sex ratio Male/ Female (% males)	0.35 (26.2)	0.55 (35.4)	0.35 (26.0)*	0.25 (19.8)*	0.25 (20.3)*	0.19 (15.9)**	< 0.0001
Episode of gastro- enteritis before the onset of dyspeptic symptoms, n (%)	59 (4.06)	8 (2.3)	18 (3.9)	10 (5.3)	5 (3.8)	8 (7.5)**	0.10
GIQLI	83.7 (± 22.4)	97.0 (± 20.2)	84.1 (± 20.8) *	74.8 (± 20.7) **	76.5 (± 20.7) **	64.4 (± 18.2) **†‡	< 0.0001

Chapter 8

HADS	15.5 (± 7.2)	13.3 (± 7.1)	15.2 (± 6.8)*	16.1 (± 6.5)*	16.7 (± 7.1)*	19.9 (± 7.5) *†‡¶	< 0.0001
HADS-A	9.50 (± 4.3)	8.29 (± 4.2)	9.4 (± 4.2)*	9.6 (± 3.9)*	10.4 (± 4.1)*	11.7 (± 4.3) *†‡	< 0.0001
HADS-D	6.00 (± 4.0)	5.01 (± 3.9)	5.78 (± 3.8)*	6.51 (± 3.8)*	6.36 (± 4.1)*	8.17 (± 4.4) *†¶	< 0.0001
PSQI	7.87 (± 3.9)	6.81 (± 3.7)	7.87 (± 3.7)*	8.18 (± 3.8)*	8.69 (± 4.2)*	9.73 (± 3.9) *†‡	< 0.0001
ISI	11.0 (± 6.5)	9.01 (± 6.1)	10.8 (± 6.3)*	11.9 (± 6.4)*	12.3 (± 6.7)*	14.1 (± 6.0)**†	< 0.0001
BMI: body mass index, BPS: bladder pain syndrome, GIQLI: GastroIntestinal Quality of Life Index, HADS: Hospital Anxiety and Depression Scale, HADS-A and HADS-D: HADS Anxiety and Depression subscales respectively, IBS: irritable bowel syndrome, ISI: Insomnia Severity Index, n: number, PSQI: Pittsburgh Sleep Quality Index, SD: standard deviation. Continuous variables are expressed as mean score ± SD. The last column indicates p-values of the global ANOVA. The symbols *, †, ‡ and ¶ indicate p-values < 0.05 vs “symptomatic controls”, FD alone patients, FD-IBS patients, or FD-BPS patients, respectively. [§] There are 11 missing values for BMI.							

Prevalence of bladder pain syndrome in patients with functional dyspepsia

Bladder pain syndrome was found in 16.0% of patients not fulfilling Rome criteria for FD, 22.2% of FD alone patients and 36.4% of FD+IBS patients. Bladder pain syndrome was therefore more prevalent among patients with FD diagnosis compared to those not fulfilling Rome criteria for FD in the entire cohort (26.9 vs 16.0% respectively, $p < 0.0001$). Bladder pain syndrome was also more prevalent among patients overlapping FD and IBS compared to those with FD alone (22.2% of those with FD alone versus 36.4% of those with FD-IBS overlap, OR 2.00 [95% CI: 1.47-2.72], $p < 0.0001$).

In multivariate analysis, factors independently associated with overlapping BPS in FD patients were altered QoL and overlap with IBS and explained 6% of the variance, while other factors (age, psychological distress, BMI, sleep quality, and gender) were not. Results are shown in Supplementary Table 5.3 in Addendum 5. Supplementary data for Article 5.

Differences between diagnostic groups

Overall results are presented in Figure 8.2 and detailed in Table 8.2. Groups differed in age, BMI, sex ratio, QoL, anxiety-depression, and sleep quality ($p < 0.05$ for all). Female predominance increased with increasing number of diagnostics ($p < 0.0001$). The QIGLI score in “symptomatic controls” was 97.0 and decreased to 84.1 in FD alone patients ($p < 0.0001$). The GIQLI decreased while insomnia and the HADS increased with the number of diagnostics. Similar results to those with HADS were shown for anxiety and depression subscales separately. The alteration of sleep quality increased with the number of diagnostics.

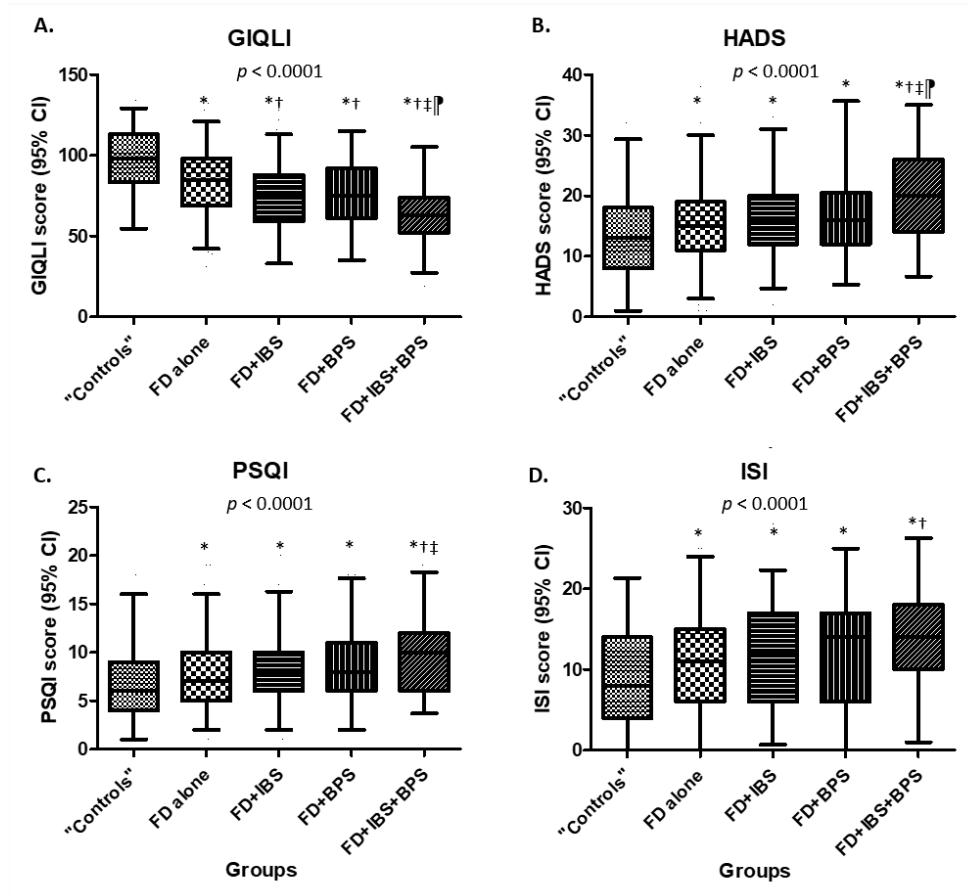


Figure 8.2. Different characteristics of the population according to the group. Comparisons of (A) GastroIntestinal Quality of Life Index (GIQLI), (B) Hospital Anxiety and Depression Scale (HADS), (C) Pittsburgh Sleep Quality Index (PSQI), and (D) Insomnia Severity Index (ISI) between the five different diagnostic groups ("symptomatic controls", FD without overlap (FD alone), FD with IBS (FD-IBS), FD with BPS (FD-BPS) and FD with both IBS and BPS (FD-IBS-BPS)). Results are presented as whiskers with 95% confidence interval (CI). All global ANOVA p -values are < 0.0001. The symbols *, †, ‡ and ¶ indicate p -values < 0.05 vs "symptomatic controls", FD alone patients, FD-IBS patients, or FD-BPS patients, respectively. "Controls" stands for "symptomatic controls" in the legend on x axis. BPS: bladder pain syndrome, FD: functional dyspepsia, IBS: irritable bowel syndrome.

There was a difference between all groups for symptoms of postprandial fullness, abdominal pain, bloating, nausea and belching between groups ($p < 0.005$ for all), with increased scores when the number of diagnostics increased, but not for regurgitations, early satiety and vomiting ($p = 0.39, 0.18$ and 0.35 respectively). Data concerning symptoms are presented in Figure 8.3.

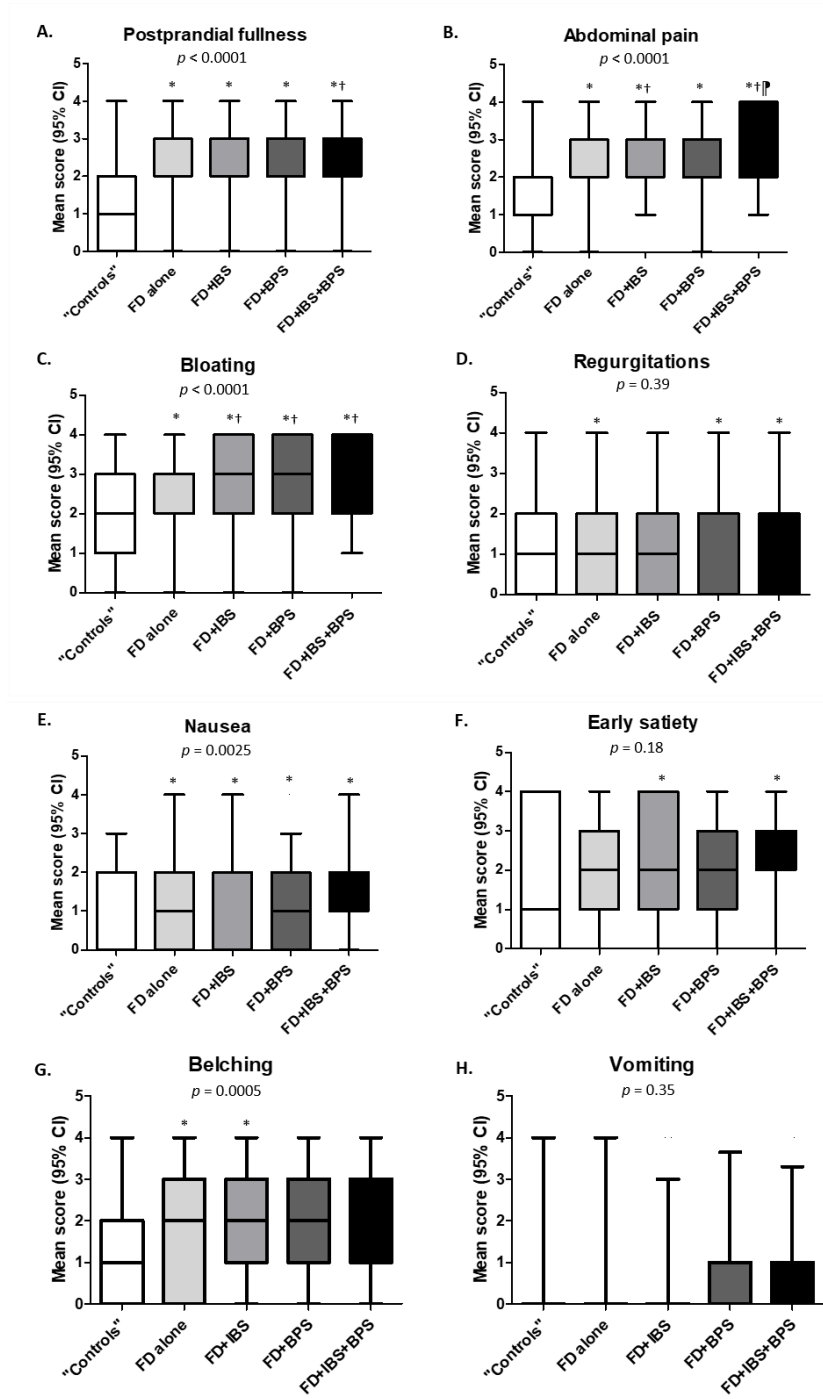


Figure 8.3. Comparison of dyspeptic complaints severity between groups.

Comparisons of the mean scores of each dyspeptic symptom in the past 15 days between the five different diagnostic groups ("symptomatic controls", FD without overlap syndrome (FD alone), FD with IBS (FD-IBS), FD with BPS (FD-BPS) and FD with both IBS and BPS (FD-IBS-BPS)): (A) postprandial fullness, (B) abdominal pain, (C) bloating, (D) regurgitations, (E) nausea, (F) early satiety, (G) belching and (H) vomiting. Symptoms were graded from 0 to 4 using a 5-point Likert scale, with 0 corresponding to their absence and 4 to extremely severe symptoms. Results are presented as whiskers with 95% confidence interval (CI). Global ANOVA p-values are mentioned below titles. The symbols *, †, ‡ and ¶ indicate p-values < 0.05 vs "symptomatic controls", FD alone patients, FD-IBS patients, or FD-BPS patients, respectively. "Controls" stands for "symptomatic controls" in the legend on x axis. BPS: bladder pain syndrome, FD: functional dyspepsia, IBS: irritable bowel syndrome.

Subgroup analysis of gastric emptying

Gastric emptying was available for 227 FD patients. Among FD alone patients, 70 (48.3%) out of 145 patients had delayed GE, with a mean GE half time of 176.8 minutes (SD: $\pm$ 84.9). Likewise, 37 (45.1%; $p = 0.67$) out of 82 FD patients with either BPS and/or IBS overlap, with a mean GE half time of 186.9 minutes (SD: $\pm$ 110.5) ($p = 0.61$).

8.7. Discussion

In the present study, we reported for the first time an association between FD and BPS. We showed BPS to be present in 26.9% of all FD patients, and even 36.4% of patients with FD-IBS overlap, in our cohort, while it was only 6.1% in patients referred for dyspeptic symptoms but who did not fulfil Rome criteria. Overlap with BPS was associated with reduced QoL, higher anxiety and depression levels, and altered sleep quality in FD patients. The impact of this overlap is even greater when considering IBS as an additional overlap diagnosis. Furthermore, we did not find any association between overlap diagnostics, including BPS, and GE half time.

Our results are in accordance with other publications in the field (Aziz et al., 2018a). The proportion of overlap with IBS in our FD population is similar to the 38.3% found recently in a large Danish study using Rome III criteria for FD (Rasmussen et al., 2015). Overactive bladder is common in FD patients, with a prevalence of about 20% (Matsuzaki et al., 2012); since OAB and BPS may share urinary symptoms (Ackerman et al., 2019), a large prevalence of BPS in FD patients was expected. However, the diagnosis of BPS is probably underestimated in clinical practice. Indeed, the prevalence of unspecified diseases of the urinary tract was around 2-3% among FD patients based on ICD10 diagnoses in the UK (Garcia-Etxebarria et al., 2022).

We found that the five groups differed overall on sex ratio, QoL, dyspeptic symptom severity, anxiety-depression and sleep. Globally, the presence of overlap with BPS or IBS in FD is associated with younger age, increased female predominance, reduced QoL, increased symptom severity, higher anxiety and depression levels, and altered sleep. Even if an increased severity of psychopathological features and a lower QoL were already reported in the literature for FD-IBS overlap (Kaji et al., 2010, Piacentino et al., 2011), it has never been reported for the overlap with BPS to our knowledge. The presence of overlaps in FD patients identifies a subgroup of dyspeptic patients with more severe disease and which deserves likely broader management. Interestingly, assessing IBS comorbidity in BPS patients has been reported to be clinically relevant since IBS comorbidity predicted poor outcome to bladder hydrodistension, a treatment often used in this urinary disorder (Niimi et al., 2016). Impact on treatment outcomes of BPS overlap in FD patients with or without IBS remains however unknown. Female predominance in BPS overlap syndromes was expected since it is commonly reported for both IBS (Canavan et al., 2014) and FD (Koloski et al., 2002), and since women report more frequently lower urinary tract symptoms compared to men (Apostolidis et al., 2009).

In our study, QoL was further altered in FD patients with overlap and dyspeptic symptom severity was increased among FD patients if an overlap with BPS and/or IBS was present, with the more comorbidities the more severe symptoms globally. It has already been shown that FD and FD-IBS overlap impairs QoL compared to the general population and FD patients without overlap respectively (Aro et al., 2011, Aziz et al., 2018b). In patients with BPS, the presence of IBS is also known to be associated with worse QoL (Suskind et al.,

2013b). Likewise, patients with FD-IBS overlap experience more severe symptoms compared to patients with FD or IBS alone (von Wulffen et al., 2019). More generally, overlaps between DGBI are associated with increased disease severity and poorer QoL (Sperber et al., 2022). Severity of the symptoms is also known to be associated with anxiety/depression comorbidity (Pinto-Sanchez et al., 2015). We have shown in our study that overlaps with IBS and/or BPS further strengthen the association between FD and anxiety-depression. This association has already been reported in the literature concerning FD patients (Vu et al., 2014), especially in the PDS subgroup (Aro et al., 2009). Patients with FD-IBS overlap have also higher depression scores (Pinto-Sanchez et al., 2015, Choi et al., 2017). Concomitant psychiatric disorders have also been associated with lower QoL (Tse et al., 2010). Furthermore, although not studied in depth in our report, life stress events have been shown to be associated with IBS and FD and may participate to higher depression scores in patients with FD-BPS overlap (Koloski et al., 2005b).

Mechanisms of overlap between DGBI and BPS are poorly understood. Visceral hypersensitivity is common in DGBI, particularly IBS (Naliboff et al., 1997) and FD (Mertz et al., 1998b), and functional bladder disorders, OAB and BPS being hypothesised to represent a continuum of a bladder hypersensitivity syndrome (Lai et al., 2014). However, even if cross-organ visceral sensitisation is well described between bladder and colon (Langlois et al., 2017), the presence of cross-organ visceral sensitisation between the upper GI tract and bladder has never been investigated to our knowledge. On the other hand, common psychological comorbidities are found in both patients with DGBI and BPS, which is confirmed by our study, but knowing if they are a cause or a consequence of both disorders is debated. Altered brain-gut interactions have been described in IBS (Ducrotte, 2009) and FD (Mearin et al., 1991), but neuroimaging studies are scarce in BPS, especially when overlapping with GI symptoms (Twiss et al., 2009). Interestingly, a history of “bladder and bowel dysfunction” in childhood has been suggested to predict an IBS-like phenotype in BPS patients (Doiron et al., 2017). However, a prospective evaluation of the onset of these disorders would be necessary to understand the natural history and risk factors of these overlaps (Homma, 2014). Recently, IBS has been shown to increase the risk of developing BPS in a 12-year follow-up (Chang et al., 2021). Sympathetic nervous system dysfunction, with sympathetic predominance, is also recognised in both IBS and BPS (Martinez-Martinez et al., 2014), suggesting a common underlying

pathogenesis in both conditions (Kim and Chang, 2012). Finally, somatisation is a risk factor for multiple DGBI but was not assessed in our work.

One limitation of our study is that our population is composed of both Rome III and Rome IV cohorts. 971 (66.8%) patients were classified according to Rome III criteria, whereas 482 (33.2%) were categorised according to Rome IV criteria. However, BPS diagnoses were equally present in both cohorts. In addition, Rome III and Rome IV criteria for FD are quite similar with marginal changes. Another limitation of our study includes the retrospective analysis, although questionnaires, symptoms and QoL scores were acquired prospectively. In addition, our study was monocentric, from a tertiary centre. Data acquired from our study may not be directly widespread to the general population.

8.8. Conclusion

In conclusion, an overlap between FD and BPS is found in 26.9% of FD patients in our cohort. A diagnosis of BPS is associated with decreased QoL, altered anxiety-depression scale and altered sleep in FD patients. Overlap with IBS further impacts all dimensions in FD patients. The benefit on those dimensions of BPS treatment in FD patients should be assessed.

8.9. Concluding paragraph

Summary of the main findings

- Bladder pain syndrome is present in 26.9% of FD patients:
 - 16.0% of the patients not fulfilling diagnostic criteria for FD;
 - 22.2% of patients with FD alone;
 - 36.4% of patients with overlapping FD and IBS.
- Overlapping BPS in FD is associated with higher dyspeptic symptom severity, anxiety, depression and insomnia levels, and with reduced QoL.
 - results even more pronounced in case of overlap with IBS.

Inferences

- Bladder pain syndrome is frequent among FD patients and should be assessed like GORD and IBS.
- Overlap syndromes with BPS and/or IBS are associated with higher dyspeptic symptom severity, reduced QoL, higher anxiety and depression levels, and greater sleep impairment.

Perspectives

- Confirm our results with BPS diagnosis confirmed by urological assessment (including urinalysis and cystoscopy).
- Investigate the impact of treating BPS in FD patients.

Dissemination

- The data presented in this chapter have been published online in *Neurogastroenterology & Motility* in 2022.

Fabien Wuestenberghs, Maximilien Baron, Chloé Melchior, Charlotte Desprez, Jean-Nicolas Cornu, Anne-Marie Leroi, Guillaume Gourcerol. Overlaps with bladder pain syndrome and irritable bowel syndrome are associated with higher symptom burden and reduced quality of life in functional dyspepsia. *Neurogastroenterology & Motility* 2022; 34 (11): e14414. <https://doi.org/10.1111/nmo.14414> (IF = 3.96)
© 2022 John Wiley & Sons Ltd.
- A graphical abstract summarised the main findings of the article (see Addendum 5. Supplementary data for Article 5).
- The content of the manuscript has been presented orally in preliminary form at the meeting of the European Society of Neurogastroenterology and Motility, NeuroGASTRO 2019, in Lisbon, Portugal:

Chapter 8

Fabien Wuestenberghs, Maximilien Baron, Chloé Melchior, Charlotte Desprez, Jean-Nicolas Cornu, Anne-Marie Leroi, Guillaume Gourcerol. Irritable bowel syndrome and bladder pain syndrome comorbidities are associated with altered quality of life, anxiety, depression and sleep in patients with functional dyspepsia [abstract 265]. *Neurogastroenterology & Motility* 2019 ; 31 (S4) : e13671. Special issue: Abstract Supplement for NeuroGASTRO 2019 Congress, September 5-7, 2019, Lisbon, Portugal <https://doi.org/10.1111/nmo.13671>

- Key messages from our work were shared on Twitter :
 - Wuestenberghs, F. [@wuefab] (2022). Our work showing that #bladder pain syndrome affects about one quarter of patients suffering from functional #dyspepsia in tertiary care is now online @NGMJJournal: <https://doi.org/10.1111/nmo.14414> @MelchioChloe @CharlotteDespr3 @JnCornu #DGBI [Twitter] 25 May]. Available on: <https://twitter.com/wuefab/status/1529445201584037892> (Consulted on: September 12, 2022).
 - Neurogastro & Motil [@NGMJJournal] (2022).  Bladder pain syndrome is present in 26.9% of functional dyspepsia patients, associated w/  GI, psychological distresses & sleep symptom burdens,  QoL Read more in November's @NGMJJournal:  <https://bit.ly/3NAJx2Q> [Twitter] 2 November]. Available on: <https://twitter.com/NGMJJournal/status/1587821843519574016> (Consulted on: November 03, 2022).

Impact of the research

- This paper has been cited 1 time [ consulted on March 16, 2023]
- The Altmetric score is 5 [ consulted on March 16, 2023].



Chapter 9 METHODS USED FOR EXPERIMENTAL PROJECTS

9.1. Animal models of visceral hypersensitivity

EXPERIMENTAL STRESS-INDUCED VISCERAL PAIN MODELS target different periods throughout the animals' lifespan (from early life to adulthood), with stressors mimicking vulnerability, trigger, or perpetuating factors influencing the development of visceral hypersensitivity in humans. **Stressors** can be directed to the CNS (exteroceptive stress: psychological or neurogenic) or to the gut (interoceptive stress: physical or systemic (Sawchenko et al., 2000). A classification of the available models is proposed in Table 9.1.

Table 9.1. Overview of available animal models of visceral hypersensitivity, classified according to the insult's period and target.

	Early life	Adulthood
CNS-directed (exteroceptive)	maternal separation stress	single prolonged stress
	water avoidance stress	water avoidance stress
	unpredictable stress	heterotypic stress
		partial restraint stress
Gut-directed (interoceptive)	colonic inflammation	colonic inflammation
	noxious CRD	somatic injuries
		intestinal infection
		antibiotics
CNS: central nervous system, CRD: colorectal distensions.		

The genetics and epigenetics of the animals could play a role. The Wistar Kyoto (WKY) and the Flinders Sensitive Line rat strains are validated models of genetic predisposition to visceral hypersensitivity (O'Malley et al., 2014). Those strains are known to exhibit increased anxiety and depression levels or to have a higher stress response, which mimics perpetuating factors found in humans with DGBI. The role of epigenetics, alterations of gene activity without any change in the deoxyribonucleic acid (DNA) sequence, has recently been extensively reviewed in this context (Zhou and Verne, 2022).

Possible stressors during **early life** are maternal separation stress, unpredictable stress and repeated colonic chemical or physical insults. Neonatal maternal separation stress in rodents mimics childhood trauma (Rosztoczy et al., 2003). Indeed, neglect, abuse, loss of a caregiver or life-threatening events during childhood put those children at a higher risk of developing IBS later in life (Videloock et al., 2009). Isolating pups from their mothers for a few hours each day for the first two weeks after birth results in rodents exhibiting visceral hypersensitivity to CRD in adulthood. This colonic hypersensitivity is further exacerbated by an acute stressor such as WAS, which involves isolating rodents on an island surrounded by water for one hour each day for a few days (Coutinho et al., 2002). Unpredictable neonatal stress based on the odour-attachment learning paradigm, mimicking early life stress, also induces visceral hypersensitivity (Chaloner and Greenwood-Van Meerveld, 2013, Ligon et al., 2018). Neonatal colonic inflammation caused by daily colonic administrations of mustard oil (5%) results in chronic visceral hypersensitivity (Al-Chaer et al., 2000). Butyrate-induced visceral hypersensitivity is also described in neonate rats (Asano et al., 2017b). Similarly, daily noxious CRD also induces chronic colonic hypersensitivity (Lin and Al-Chaer, 2003). Conversely, acute somatic injuries, such as saline or carrageenan injections into the legs of rodents, induce visceral hyposensitivity in adulthood (Wang et al., 2004).

Potential stressors in rodents during **adulthood** are life-threatening events, acute and chronic stress (WAS, partial restraint stress (PRS) or heterotypic stress), physical insults such as intestinal infection or inflammation, antibiotics and surgery.

Water avoidance stress and PRS, which involves preventing the movements of the rats for two hours a day, in Wistar rats mimic chronic **psychosocial stress** known to trigger the development of DGBI in humans. Water avoidance stress has been shown to provoke delayed colonic hypersensitivity to CRD (Bonaz and Tache, 1994), and PRS induces an immediate colonic hypersensitivity to CRD (Gue et al., 1997). The state of the animals before applying the stressor affects the response to WAS, with surgery and post-operative single housing being key factors (Larauche et al., 2010). Indeed, electrode implantation for electromyography (EMG) and post-surgical single housing are required for mice to develop WAS-induced visceral hypersensitivity (Larauche et al., 2010). Development of visceral hypersensitivity following WAS in

rats is mediated by microglial MAPK-p38 activation in the central nucleus of the amygdala (Yuan et al., 2020b). Heterotypic stress models, with alternating different stressors to avoid habituation to repeated exposure to the same stressor, can also induce sustained colonic hypersensitivity (Winston et al., 2010).

Single prolonged stress, a model of PTSD, provokes colonic hypersensitivity in male adult rats (Chen et al., 2022).

Intestinal infections are a proven aetiology of different DGBI. **Post-infectious models** of colonic hypersensitivity have therefore been developed: *Trichinella spiralis* infestation in mice (Bercik et al., 2004), *Nippostrongylus brasiliensis* infestation in rats (McLean et al., 1997), *Citrobacter rodentium* infection in mice (Aguilera-Lizarraga et al., 2021), and so on. Conversely, *Syphacia obvelata* (mouse pinworms) infestation decreases the severity of experimental dextran sodium sulphate (DSS)-induced colitis in male C57BL/6 mice through immunomodulatory effects (induction of Tregs and change in cytokine profiles) (Taghipour et al., 2019).

Post-inflammatory models have also been developed based on the reduced rectal pain thresholds described in IBD populations during active disease flares (Roberts et al., 2021). Chronic DSS intake in drinking water induces colonic inflammation in mice (Picard et al., 2019) and rats (Lopez-Estevéz et al., 2022). Still, colitis is not sufficient to provoke colonic hypersensitivity (Larsson et al., 2006). Intracolonic administrations of acetic acid (AA) (Burton and Gebhart, 1995, Wu et al., 2017a), mustard oil (Palecek and Willis, 2003) and zymosan (Coutinho et al., 1996) cause short-term colonic hypersensitivity in rats. Intracolonic administrations of TNBS in rats induce visceral hypersensitivity as soon as 4-5 days later, and lasts 14 days (Morris et al., 1989, Gschossmann et al., 2004, Adam et al., 2006). The TNBS colitis model is a classical model of Crohn's disease. Trinitrobenzene sulphonic acid is administered concomitantly with ethanol since the ethanol disrupts the intestinal barrier before TNBS, a hapten reagent, can interact with proteins of the colonic mucosa and then to elicit a strong response of the host immune system. About a quarter of those rats present a reoccurrence of colonic hypersensitivity 16 weeks later (Zhou et al., 2008). Visceral hypersensitivity is mediated by transient receptor potential vanilloid 1 (TRPV1) and transient receptor potential ankyrin 1 (TRPA1) pathways at both the peripheral and spinal levels during acute TNBS colitis in rats (Vermeulen et al., 2013). In contrast, serine proteases (trypsin, elastase, etc.) mediate post-

inflammatory hypersensitivity in the same model (Ceuleers et al., 2018). Daily intracolonic administrations of deoxycholic acid, a bile salt acid, also induce colonic hypersensitivity in rats during 1 week up to 4 weeks (Traub et al., 2008).

The administration of non-absorbable antibiotics (neomycin, bacitracin and pimarin) induces colonic hypersensitivity in mice *via* changes in gut **microbiota** (Verdu et al., 2006). The link between gut microbiota and visceral nociception is complex and far beyond the scope of this chapter. For example, a high-FODMAP diet increases visceral nociception in rats by inducing dysbiosis; this altered gut microbiota (increased Gram-negative bacteria) leads to increased circulation of LPS and induces intestinal inflammation, barrier dysfunction, and visceral hypersensitivity (Zhou et al., 2018). Conversely, *Faecalibacterium prausnitzii* decreases colonic sensitivity in response to CRD in two animal models of colonic hypersensitivity induced by chronic or acute stress (neonatal maternal separation stress in mice and PRS in rats) (Miquel et al., 2016).

Plantar incision of adult male Sprague-Dawley rats induces two-week-long colonic hypersensitivity, mediated by **somato-visceral convergence** in the spinal cord (Cameron et al., 2008), mimicking the development of DGBI following surgery (Li et al., 2011). Similar results were found following injections of sterile saline in the gastrocnemius muscle of rats (Miranda et al., 2004), showing that somatic pain can alter visceral sensitivity in the rat.

Finally, models of cross-organ visceral sensitisation have been developed but are described further in the next subchapter (see 9.2. Animal models of cross-organ visceral sensitisation). For example, neonatal zymosan-induced cystitis induces colonic hypersensitivity in adult rats through viscerovisceral interactions (Miranda et al., 2011).

Animal models of FD are rare, and their description is beyond the scope of this chapter. We refer the reader to a recent review on the subject for further details (Ye et al., 2018). Without being exhaustive, the normoglycaemic biobreeding rat is a spontaneous model for impaired gastric accommodation (Vanormelingen et al., 2016). Chronic stress induced by tail clamping in rats is a model of impaired duodenal barrier function (Wei et al., 2011, Chang et al., 2017). Preclinical models of gastric hypersensitivity are even rarer. They involve neonatal rats: treatment with gavages of 0.1% of iodoacetamide (Zhou et al., 2017), sequential stress (maternal separation followed by gavages of iodoacetamide) (Jing et al., 2017), gavages with iodoacetamide in the neonatal period followed by

acute restraint stress in adulthood (Sallam et al., 2015), and so on. Giving 0.1% iodoacetamide in drinking water to rats for five to seven days is an established model for inducing mild diffuse gastritis (Bielefeldt et al., 2002, Lamb et al., 2003, Painsipp et al., 2007). Gastric irritation caused by either injection of 20% AA into the stomach wall (ulcer model) or drinking water continuously supplemented with 0.1% iodoacetamide (gastritis model) in adult male rats weighing 400-500 g induces gastric hypersensitivity (increased responses to gastric distension in awake animals using EMG) (Ozaki et al., 2002). Gastric hypersensitivity has also been found to develop following iodoacetamide gavage in neonatal rats (Ouyang et al., 2020) or when combined with tail clamping in adult rats (Zhao et al., 2020). Iodoacetamide is a sulphhydryl alkylator (blocker), inducing inhibition of NOS activity in the stomach (Karmeli et al., 1996). Iodoacetamide-induced gastritis is accompanied by TRPA1 upregulation in rats (Cseko et al., 2020) and gastric hypersecretion in mice (Piqueras et al., 2003). *H. pylori*-infected mice are an alternative model of chronic gastritis (Lee et al., 1997).

Responses to the sensitisation of the bladder or the colon differ according to sex in mice and rats, respectively (Yoshiyama et al., 2008, Ji et al., 2012). Indeed, ovarian hormones, especially oestradiol, are critical modulators of visceral sensitivity. They mediate the development of visceral hypersensitivity following unpredictable early life stress in female rats, for instance (Chaloner and Greenwood-Van Meerveld, 2013). There are also sex-dependent differences in the microglia in mice (Guneykaya et al., 2018). Most studies, therefore, focus on male rodents to avoid gender and variation in hormonal status as a possible confounding factor in the interpretation of the results. There is no data about the effect of gender on cross-organ sensitisation models.

In our colon-stomach cross-activation work, we needed a localised insult, sparing the colon or stomach where necessary. We also put aside strains with a predisposition to visceral hypersensitivity and CNS-centred models. We have therefore chosen models of isolated gastric or colonic inflammations. We also decided to focus on male rats to avoid the effect of sex hormones.

9.2. Animal models of cross-organ visceral sensitisation

Some models of cross-organ visceral sensitisation have been described in the section about Cross-organ visceral sensitisation in the Introduction of this

manuscript. A summary of available animal models of cross-organ visceral sensitisation involving the GI tract is shown in Table 9.2.

Table 9.2. Overview of available animal models of cross-organ visceral sensitisation involving the gut.

Induction of disease	Animals	Secondarily impaired organ	Timing of crosstalk	References
<i>TNBS-induced colitis</i>	Rats Mice	Bladder	1 hour to 90 days	(Pezzone et al., 2005) (Xia et al., 2016) (Xia et al., 2012)
<i>Mustard oil-induced colitis</i>	Mice	Upper GI	Day 28	(Kimball et al., 2005)
<i>TNBS-induced colitis</i>	Rats (Day 10)	Stomach	5-8 weeks	(Winston and Sarna, 2013, Li et al., 2016, Winston and Sarna, 2016)
<i>Noxious CRD</i>	Mice	Bladder	> 3 hours	(Qiao and Tiwari, 2020) (Fig 1)
<i>Zymosan-induced prostatitis</i>	Mice	Bladder	Days 7-28	(Schwartz et al., 2016)
<i>Formalin-induced prostatitis</i>	Rats	Bladder	Day 7	(Funahashi et al., 2019)
<i>Zymosan-induced cystitis</i>	Rats	Colon	2-3 months	(Miranda et al., 2011)

CRD: colorectal distensions, TNBS: 2,4,6-trinitrobenzene sulphonic acid.

Adapted from Qiao and Tiwari (Qiao and Tiwari, 2020).

The criteria required for animal models of cross-organ sensitisation to be valid are (Qiao and Tiwari, 2020):

- the disease needs to be induced in a specific organ;
- functional dysfunction, in particular visceral hypersensitivity, must be found in at least one other organ than the injured/irritated one;
- and any direct injury to the cross-sensitised organ should be avoided.

9.3. Study of visceral sensitivity

The general principle of testing visceral perception is to deliver a sensory stimulus (mechanical, thermal, electric, chemical [e.g. capsaicin], or multimodal) and to measure the evoked response (Keszthelyi et al., 2012). Measuring the magnitude of response to the stimulus can be subjective (using verbal scores and scales such as the Visual Analogue Scale [VAS] to assess thresholds of sensations [first sensation, urge, pain] and its intensity in humans, or the Abdominal Withdrawal Reflex [AWR] scale in rodents), with the risk of reporting bias, or more objective (VMR, neurophysiological testing, autonomic function assessment or brain imaging). In humans, all of these techniques have been used primarily in IBS patients.

Distensions of the gastrointestinal tract & pseudo-affective reflexes

Rectal and, to a lesser extent, sigmoid distensions are the most widely used sensory stimuli to test visceral perception in humans and rodents and, in combination, are termed CRD. An **electronic barostat** maintains constant pressure or volume within an air-filled, infinitely compliant polyethylene bag and to measure variations in rectal tone by recording intrarectal pressure and volume changes. The technique was first introduced in humans by James Ritchie in 1973 (Ritchie, 1973) and rats by Timothy J. Ness and Gerald F. Gebhart (Ness and Gebhart, 1988). Several **distension protocols**, differing by the duration of inflations, the type of inflation (tonic vs phasic distensions), the risk of bias (ascending vs randomised distensions), and according to the way of measuring the response (threshold identification, rating of intensity, etc.), are available. Rectal barostat with phasic and isobaric distension protocol is more sensitive than a ramp distension protocol to assess visceral hypersensitivity in IBS patients (Josefsson et al., 2022b). Complex distension protocols, based on the non-random presentation of stimuli (e.g. double random staircase distension to reduce psychological response bias by making the stimulus unpredictable to the subject), are also available.

In humans, the assessment of visceral perception using the barostat technique is based on identifying **thresholds** for perception, which are known to be lower in IBS patients compared to healthy controls (Ritchie, 1973). There is a

poor correlation between sensitivity assessment by barostat and the severity of symptoms reported by IBS patients (Kuiken et al., 2005). The reporting of the response magnitude can be influenced by psychological factors, especially anxiety and vigilance levels, and is, therefore, subjective. The method used to assess visceral perception is essential. For example, visual analogue scales have superior psychometric properties compared to other pain scales (Price et al., 1994). Furthermore, visceral perception in IBS patients should be performed during a postprandial period rather than a fasted state. Indeed, the intraduodenal fat infusion lowers colorectal perception thresholds in IBS patients (Caldarella et al., 2005). The mechanism explaining this increased sensory response is the release of cholecystokinin by enteroendocrine cells in the intestinal mucosa in response to changes in luminal fat content; this peptide is known to increase rectal nociception in healthy volunteers (Sabaté et al., 2002) and could therefore sensitise mechanoreceptors in the colon of IBS subjects.

In rodents, CRD induce a range of autonomic and behavioural reactions called **pseudo-affective reflexes**. These responses include blood pressure and heart rate variations, passive avoidance behaviours, and contractions of the abdominal muscles (the latter being called the VMR). Assessment of the VMR is the most widely used parameter of response to visceral pain in rodents. It can be assessed visually by the AWR (Al-Chaer et al., 2000), by EMG with electrodes implanted in the external oblique muscle of the animals, or indirectly by measuring the intracolonic pressure (Larauche et al., 2009). **Visceromotor responses** to CRD disappear after the transection of the pelvic pathway but not after the transection of the splanchnic pathway in mice, suggesting that pelvic pathways mediate VMRs (Kyloh et al., 2011). Measuring the intracolonic pressure in awake rats is represented in Figure 9.1.

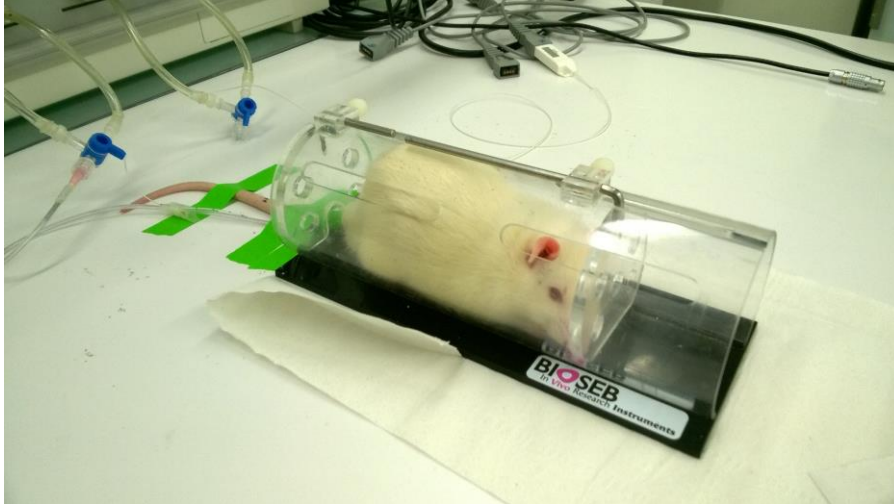


Figure 9.1. Measurement of intra-colonic pressure in an awake Sprague-Dawley rat in a restraining cage.

Similarly, gastric distensions with an electronic barostat are the gold standard for studying human **gastric sensitivity** (Azpiroz and Malagelada, 1990). The technique is invasive and very unpleasant for patients. It is also known to affect gastric physiology: acceleration of GE of liquids (Ropert et al., 1993), modification of the distribution of the meal in the stomach, the bag pushing the meal in the antrum, with subsequent antral dilatation, possibly inducing falsely increased fundic accommodation during the test (Mundt et al., 2002). A simple stepwise protocol is superior to a complex double random staircase to assess sensitivity to gastric distensions (Sarnelli et al., 2001).

Variations in blood pressure, a pseudo-affective reflex in the rat, can be measured following colonic and gastric distensions with an electronic barostat, as shown in Figure 9.2. No study compared the amplitude of response assessed by EMG, the gold-standard VMR technique, with changes in blood pressure, however.

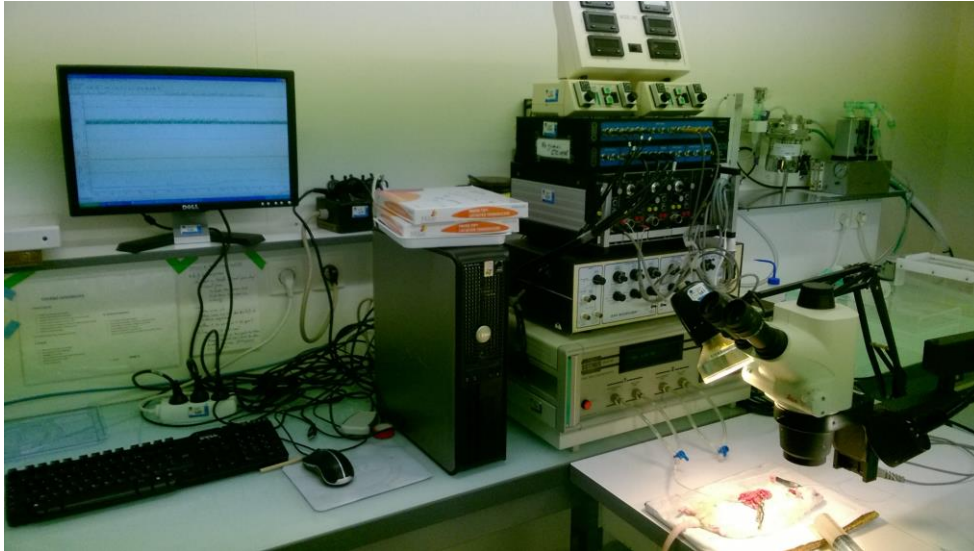


Figure 9.2. Barostat and the system for measuring the pressure in the carotid artery in a rat sedated with a barbiturate.

The barostat used is a Distender Series II™ (G&J Electronics Inc., Toronto, ON, Canada) designed for laboratory animals.

Neurophysiological tests

Neurophysiological tests (cerebral evoked potentials (CEP), magnetoencephalography (MEG) and monitoring the nociceptive flexor reflex (RIII reflex)) have also been used to assess visceral nociception in humans.

Cerebral evoked potentials are the electrical manifestation of the brain's response to an external stimulus. Following a sensory stimulus, recording an electroencephalogram (EEG) *via* surface electrodes placed on the scalp shows stimulus-specific CEP occurring at a fixed time after each stimulus (Sinhamahapatra et al., 2001). In contrast, the additional brain activity occurs randomly.

Magnetoencephalography allows the detection of cortical magnetic activity induced by postsynaptic current flow in neurons. Visceral stimulations generate minute magnetic fields in the cortex (Smith et al., 2011).

Reflex responses to painful stimulations are a marker of spinal nociceptive processes. The **flexion reflex** (nociceptive withdrawal reflex or RIII reflex) is a complex flexion reflex of the ipsilateral limb following a cutaneous stimulus. In

healthy volunteers, rapid rectal distensions facilitate the RII reflex recorded from the lower limb (Bouhassira et al., 1998). In IBS patients, the RII reflex is significantly facilitated during slow-ramp distension (whereas inhibition is seen in healthy subjects), and the inhibition induced by rapid distensions is reduced considerably (Coffin et al., 2004). All these results suggest a failure in the descending control of pain perception in IBS, leading to the hyperexcitability of spinal nociceptive neurons (see Descending control of pain perception in 1.4. Pain and visceral nociception for more details).

Further studies are necessary to validate those techniques in visceral sensitivity assessment. Although these techniques have been described in humans, electroencephalographic signatures of pain and analgesia are reported in rats (LeBlanc et al., 2016).

Measurement of autonomic dysfunction

Increased sympathetic activity is known to magnify the perception of gut stimuli (Iovino et al., 1995). Cardiac sensitivity to the baroreflex, the mechanism maintaining blood pressure at nearly constant levels through the modulation of the ANS, and cardiac vagal tone are used to measure responses of the ANS in humans (Mazurak et al., 2012). For instance, IBS patients have increased baseline cardiac sensitivity to the baroreflex compared to healthy volunteers (van der Veek et al., 2005). In rodents, real-time telemetric recordings of heart rate and **heart rate variability** enable the detection of post-laparotomy pain in mice (Arras et al., 2007).

Functional brain imaging

The rationale for using brain imaging techniques to assess visceral sensitivity is that increased neuronal activity within the brain is associated with increased neuronal metabolism and regional cerebral blood flow (rCBF). Two methods are used: **fMRI**, utilising the difference in the decay time of the magnetic resonance signal from oxyhaemoglobin and deoxyhaemoglobin, and positron emission tomography (**PET**) using ^{15}O -labeled water (H_2^{15}O) to monitor changes in rCBF, which are both correlated to regional metabolism. The validity of both techniques remains to be confirmed, however.

Brain imaging studies found activation of the homeostatic afferent network in IBS patients following CRD compared with healthy volunteers (Naliboff et al., 2006). However, there is a risk of habituation when repeated CRD are performed over time. There is also a poor correlation between these changes and symptoms in IBS patients (Larsson et al., 2012).

Functional MRI and micro-PET (mPET) scanning can also assess nociception in the CNS during rectal distension in rats (Zhu et al., 2014, Kim et al., 2016).

Other methods

Other methods have been described in humans to assess visceral sensitivity:

- **Satiety drink tests** have been proposed as a non-invasive alternative to test gastric hypersensitivity. The technique is reproducible and correlated with barostat results (Tack et al., 2003);
- **Capsaicin** is used to assess chemical hypersensitivity of the stomach in FD (Fuhrer et al., 2011);
- **Clinical assessment** by questioning IBS patients about pain location could inform clinicians of visceral hypersensitivity. Indeed, the site of the pain is different between hypersensitive and normosensitive patients, with pain located outside one of the two iliac fossae suggesting that a patient is normosensitive (Melchior et al., 2018);
- Scoring GI symptoms during **nutrient infusion** in the stomach can also evaluate gastric perception in humans (Masuy et al., 2019);

and in rodents:

- Visceromotor response to the administration of hydrochloric acid (HCl) in the stomach of awake rats can assess gastric sensitivity (Schuligoi et al., 1998, Lamb et al., 2003);
- **Behavioural responses** can also detect visceral pain in rodents: burrowing activity, the rat grimace scale, a composite behaviour score (Leung et al., 2019), vocalisations to CRD and anxiety-like behaviour (Ji et al., 2015) in rats, and automated behaviour analysis in mice (Hayashi et al., 2011), among other methods.

9.4. Study of intestinal permeability

Intestinal epithelial barrier

The digestive mucosa is exposed to numerous antigens, the diet, and commensal and pathogenic microbes. The intestinal barrier comprises an epithelial (physical) barrier composed of mucus, a cellular layer and the mucosal immune system. This barrier protects the organism against the luminal contents and pathogens, although it enables water, nutrient and ion transports, and it is immunotolerant to commensal microorganisms.

The **mucus layer** comprises mucins secreted by goblet cells and prevents large particles and intact bacteria from coming into contact with the epithelium. The **apical junctional complex** (Odenwald and Turner, 2017) holds epithelial cells together to form a continuous monolayer and is composed of a network of tight junctions (claudins and tight junction-associated MARVEL^c proteins (TAMPs), which include occludins) (Van Itallie and Anderson, 2014), adherens junctions (epithelial cadherin (E-cadherin), α - and β -catenin's) and desmosomes (desmoglein and desmocollin), as shown in Figure 9.3. Tight junctions are connected to the actin cytoskeleton *via* cytosolic proteins (zonula occludens-1 (ZO-1), ZO-2, ZO-3, catenin's and desmoplakin), whereas desmosomes are connected to intermediate filaments composed of keratins. Regulatory proteins are also involved, such as zonulin.

^c The MARVEL (MAL and related proteins for vesicle trafficking and membrane link) conserved domain comprises four transmembrane helices and is involved in membrane apposition events. The MARVEL domain-containing proteins belong to the myelin and lymphocyte (MAL), physins, gyryns and occludin families.

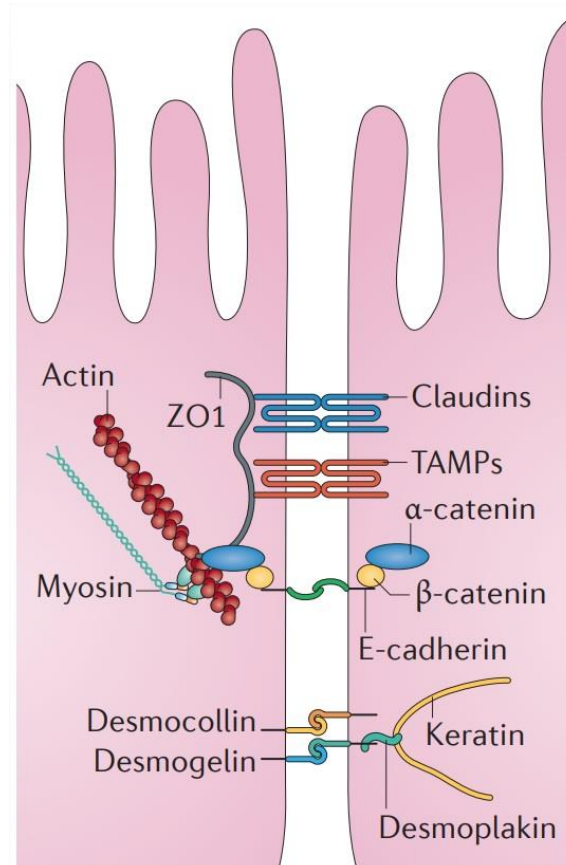


Figure 9.3. The apical junctional complex.

Junctional transmembrane proteins are composed of tight junctions, adherens junctions and desmosomes, which are connected to the actin cytoskeleton and intermediate filaments.

Adapted from Odenwald et al. (Odenwald and Turner, 2017) by permission from Springer Nature. Copyright © 2016 Nature Publishing Group, a division of Macmillan Publishers Limited. All Rights Reserved.

Alterations of gut barrier in disorders of gut-brain interactions

Intestinal permeability is the opposite of the intestinal barrier function, enabling fluxes through the epithelium. Paracellular permeability pathways include the *pore* and *leak* pathways in intact epithelia, whereas the *unrestricted* pathway is the main route when the epithelia are damaged, for example, after

DSS or TNBS colitis in rodents. In healthy state, gut microbes promote nerve secretion of CGRP via stimulation of nociceptors on nerve endings; CGRP then stimulates goblet cells to produce mucus (MUC2 mucins) which helps maintain mucosal integrity (Yang et al., 2022a). Conversely, dysbiosis could lead to a disruption of this protective mechanism and lead to an increase in gut permeability.

Increased intestinal permeability (also termed *leaky gut*) is described in IBS patients and different animal models of this disorder. One hypothesis concerning the pathophysiology of IBS and FD suggests that increased mucosal permeability in the gut could lead antigens to pass the gut barrier and activate the mucosal immune system (both innate and adaptive responses) in genetically predisposed subjects, probably with modulation by the gut microbiota (Talley, 2020). This low-grade mucosal inflammation, with the local release of inflammatory mediators, would lead to the development of digestive symptoms (motor dysfunction with subsequent transit disorders and the activation of nerve endings with subsequent pain) and extra-digestive manifestations (anxiety, depression, fatigue, etc.) through circulating proinflammatory cytokines (Talley, 2020). However, it seems more likely that the inflammatory response is only one of many factors involved in the disorder's pathogenesis.

Patients suffering from FD also have increased duodenal mucosal permeability, as assessed by Ussing chambers (Vanheel et al., 2014).

Methods to assess gut permeability

Permeability of the GI tract can be assessed *in vivo* or *in vitro*.

Non-invasive techniques

The measurement of intestinal permeability is based on the ratio of urinary excretion of different sugars (disaccharides and monosaccharides) (Mishra and Makharia, 2012). After the measurement of concentrations of the sugar probes in the urine, the results are expressed as the ratio of the percentage of excretion of the ingested doses of the sugars. Lactulose and mannitol are the most commonly used to assess small bowel permeability, with results expressed as the **lactulose:mannitol ratio** (LMR = % lactulose/% mannitol). Alternatives are lactulose/L-rhamnose and cellobiose/mannitol. Methods to assess whole gut

permeability use ^{51}Cr -ethylenediaminetetraacetic acid (EDTA)/mannitol, sucralose/mannitol and sucralose/L-rhamnose combinations.

Ussing chambers

Ussing chambers are named after Danish physiologist Hans Henriksen Ussing, who described his *little chamber* in 1951, the founding point of epithelial physiology. Each acrylic chamber consists of two half-chambers: one with stainless steel needles welcoming the tissue (mucosal/apical side of the tissue in contact with this half-chamber) and the other with orifices (serous/basal side) to accommodate the needles of the other half-chamber. The upper part of the half-chambers has perforations (the largest is to introduce the solutions to be analysed, and the smallest to allow the tissue to be oxygenated using cones (gas = ambient air, 78% N_2 and 21% O_2), with the rise of the bubbles through the orifices demonstrating the oxygenation of the buffer solution (HBSS, Hank's Balanced Salt Solution), making it possible to prolong the *lifespan* of the tissues during the manipulation. The most classic method involves using a *whole-thickness* tissue, although the ideal would be to use only the mucosa. The compound used to study permeability can be **fluorescein isothiocyanate (FITC)-dextran** (4 kDa) or a combination of **Lucifer yellow**, which is a smaller molecule (457 Da), and **Alexa Fluor™**, a heavier molecular, because it is bioconjugated to dextran (3-10 kDa). The measurement of the intensity of fluorescence on the serous side after three hours will be proportional to the permeability of the tissue, which will let the compound used move from the mucosal side to the serous side. This technique is, therefore, mainly used to study paracellular transport.

Fluorescein isothiocyanate is a fluorescent dye belonging to the xanthene dyes group, while Lucifer yellow belongs to isoquinolines, and Alexa Fluor™ is a carboxylic acid. The result obtained with the plate reader or spectrofluorometer (the technique used being fluorescence spectroscopy) following the FITC-dextran assay after the Ussing chamber procedure, for example, is a fluorescence intensity, expressed in arbitrary units (AU), the absolute value of which differs depending on the plate reader used. The FITC-dextran range enables unknown concentrations to be interpolated. The same principles also apply to Lucifer yellow and Alexa dyes.

The alternatives in mice are to gavage them with FITC-dextran or ovalbumin, and to assess the concentrations of these compounds in the rodents'

blood by flow cytometry, with samples taken by cardiac or tail vein punctures, respectively (Tsai et al., 2023).

We assessed colonic and gastric permeabilities in our works using Ussing chambers with FITC-dextran in mice, and Lucifer yellow and Alexa dyes in rats.

Transepithelial electrical resistance

Transepithelial electrical resistance (TEER) is the measurement of electrical resistance across a cellular monolayer, reflecting this layer's integrity and permeability. The technique is increasingly used to assess permeability through barrier model systems (Srinivasan et al., 2015).

Other methods

Indirect methods are also able to assess gut permeability:

- The expression levels of tight junction proteins (ZO-1, claudin-1, occludins, etc.) assessed by western blot (WB) analysis reflect intestinal permeability (Volynets et al., 2016);
- Circulating biomarkers of altered intestinal barrier function include zonulin, intestinal fatty acid binding protein (I-FABP), diamine oxidase (DAO), LPS, LPS binding protein (LBP), IL-6 and IL-8 assessed by enzyme-linked immunosorbent assay (ELISA);
- Faecal biomarkers of altered intestinal barrier include zonulin, secretory immunoglobulin A (sIgA), calprotectin and eosinophil-derived neurotoxin;
- Qualitative methods to assess intestinal permeability include the visualisation of tight junctions using freeze-fracture electron microscopy and immunostaining of tight junctions' proteins (occludins, ZO-1, etc.) (Van Itallie and Anderson, 2014).



Chapter 10 ARTICLE 6. DEVELOPMENT OF A CHRONIC BLADDER-COLON CROSS-SENSITISATION MODEL IN MICE

10.1. Introductory paragraph

Articulation with previous projects

The work prior to my arrival in my host laboratory concerned bladder-colon interactions. Indeed, IBS and BPS are commonly found to overlap in clinical practice, and are both characterised by visceral hypersensitivity. Since pelvic organs share common sensory pathways, it was likely that those syndromes involved a cross-sensitisation process between the bladder and the colon, but the precise pathophysiology remained poorly understood. The animal model used for bladder-colon cross-sensitisation enabled me to learn the methods used to study visceral pain in laboratory animals.

What is already known?

Models of acute bladder-colon and colon-bladder cross-sensitisation are described.

Research questions

- Can experimental cystitis induce colonic hypersensitivity?
- If applicable, which pathway(s) are involved in the bladder-colon cross-sensitisation?

Aims

- Develop a model of chronic bladder-colon cross-sensitisation.
- Investigate the mechanisms involved in the cross-sensitisation.

Methodology

- Animals: 8-weeks-old male C57BL/6 mice weighing 22-26g
- Ultrasound-guided intravesical (IV) injections of AA
- Colorectal sensitivity assessed in conscious mice by measuring intracolonic pressure during isobaric CRD

Chapter 10

- Tissue inflammation: MPO
- Tissue permeability: Ussing chambers
- Neuronal activation: c-Fos protein expression assessed in the spinal cord (L6-S1 level) using immunohistochemistry
- CX3CR1^{gfp+} mice to identify and count microglial cells in the L6-S1 dorsal horn of the spinal cord
- Expressions of NK1R and MAPK-p38 in the spinal cord: WB
- Pharmacological studies using intracerebroventricular (ICV) and/or intrathecal (IT) injections of minocycline, CP 99994, SB203580 or saline

My contribution

The content of this article relates the thesis project of Karim Atmani. I participated in the analysis of the data, I drafted the manuscript and critically reviewed the manuscript for important intellectual content.

10.2. Title page

Complete title

Bladder-colon chronic cross-sensitisation involves neuro-glial pathways in male mice

Short title

Bladder-colon cross-sensitisation

Authors

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10.3. Abstract

Background/Aims

Irritable bowel syndrome (IBS) and bladder pain syndrome (BPS) often overlap and are both characterised by visceral hypersensitivity. Since pelvic organs share common sensory pathways, it is likely that those syndromes involve a cross-sensitisation of the bladder and the colon. The precise pathophysiology remains poorly understood. The aims of this study were to develop a model of chronic bladder-colon cross-sensitisation and to investigate the mechanisms involved.

Methods

Chronic cross-organ visceral sensitisation was obtained in C57BL/6 mice using ultrasound-guided intravesical injections of acetic acid under brief isoflurane anaesthesia. Colorectal sensitivity was assessed in conscious mice by measuring intracolonic pressure during isobaric colorectal distensions. Myeloperoxidase, used as a marker of colorectal inflammation, was measured in the colon, and colorectal permeability was measured using Ussing chambers. c-Fos protein expression, used as a marker of neuronal activation, was assessed in the spinal cord (L6-S1 level) using immunohistochemistry. Green fluorescent protein on the fractalkine receptor-positive mice were used to identify and count microglial cells in the L6-S1 dorsal horn of the spinal cord. The expression of NK1 receptors and MAPK-p38 were quantified in the spinal cord using western blot.

Key results

Visceral hypersensitivity to colorectal distension was observed after the intravesical injection of acetic acid vs saline ($p < 0.0001$). This effect started one hour post-injection and lasted up to seven days post-injection. No increased permeability or inflammation was shown in the bladder or colon seven days post-injection. Visceral hypersensitivity was associated with the increased expression of c-Fos protein in the spinal cord ($p < 0.0001$). In green fluorescent protein on the fractalkine receptor-positive mice, intravesical acetic acid injection resulted in an increased number of microglial cells in the L6-S1 dorsal horn of the spinal cord ($p < 0.0001$). NK1 receptor and MAPK-p38 levels were increased in the spinal cord up to seven days after injection ($p = 0.007$ and 0.023 respectively). Colorectal sensitisation was prevented by intrathecal or intracerebroventricular injections of

minocycline, a microglia inhibitor, by intracerebroventricular injection of CP99994 dihydrochloride, a NK1 antagonist, and by intracerebroventricular injection of SB203580, a MAPK-p38 inhibitor.

Conclusions

We describe a new model of cross-organ visceral sensitisation between the bladder and the colon in mice. Intravesical injections of acetic acid induced a long-lasting colorectal hypersensitivity to distension, mediated by neuroglial interactions, MAPK-p38 phosphorylation and the NK1 receptor.

10.4. Introduction

IRITABLE BOWEL SYNDROME AND BPS are two functional disorders affecting the GI tract and the urinary tract, respectively (Alagiri et al., 1997, Nickel et al., 2010). Their prevalence in the general population is 4.6% (Palsen et al., 2020) and 4.2% (Suskind et al., 2013a), respectively, and recent studies have shown a strong overlap between both syndromes (Alagiri et al., 1997, Nickel et al., 2010). Indeed, BPS is found in 40-60% of IBS patients (Mathieu, 2009), and IBS is observed in 25.4-38.6% of BPS patients (Alagiri et al., 1997, Nickel et al., 2010). Both syndromes are characterised by visceral mechanical hypersensitivity at the urinary tract level for BPS and at the intestinal level for IBS (Naliboff et al., 1997, Lai et al., 2014). The involvement of several mechanisms has been suggested in the onset and/or the maintenance of visceral hyperalgesia, including urothelial and/or intestinal epithelial permeability, mucosal immune activation and altered brain-gut interaction (Barbara et al., 2011).

Despite increasing knowledge of the pathophysiology of IBS and BPS, limited mechanistic data is available in the context of BPS-IBS overlap. Based on the fact that pelvic organs share common sensory pathways, a few studies have offered evidence that cross-sensitisation between the bladder and the colon may explain sensitisation of both organs (Langlois et al., 2017). This may involve primary extrinsic afferents or central sensitisation, both at the spinal and supraspinal levels (Brumovsky and Gebhart, 2010). All these studies involved acute sensitisation models, often in anaesthetised animals (Pezzone et al., 2005) ; therefore, there is not yet any data regarding the chronicization of pelvic organ cross-sensitisation.

The role of spinal glia has recently been highlighted in the sensitisation of the bladder or colon (Bradesi et al., 2009) and even in cross-organ sensitisation between both organs (Qiao and Tiwari, 2020). The role of spinal glia, however, has never been demonstrated in the maintenance of such sensitisation using models of bladder-colon cross-sensitisation induced chronic visceral hyperalgesia. Therefore, our study aimed to develop a model of chronic cross-organ sensitisation between the bladder and the colon and to investigate the mechanisms involved in the development and persistence of this cross-sensitisation.

10.5. Materials and methods

Ethics

The experiments were carried out in accordance with the ethical guidelines of the IASP (Zimmermann, 1983) and in accordance with the policies of the French Ministry of Agriculture and Fisheries (Decree No. 874848). The local Ethics Committee approved our protocol for Animal Experiments (CENOMEXA Number: N/02-01-13/02/01-16).

Animals

Adult male wild-type C57Bl/6 mice (Janvier Laboratories, Le Genest-Saint-Isle, France) and transgenic mice expressing the green fluorescent protein on the fractalkine receptor of microglial cells (CX3CR1^{gfp+} mice; INSERM Laboratory U1239, Dr David Vaudry team, Mont Saint Aignan, France (Brifault et al., 2015)) were eight weeks old on the day of the experiment (weight range: 22-26g). The animals were randomised by their weight in several cages, with five mice per cage, housed in a 12-hour light/dark cycle in an animal housing facility free of specific pathogenic organisms and maintained at room temperature (22 ± 2°C). The animals received a standard diet (RM1 diet; SDS, Witham, Essex, UK). Drinking water and food were available *ad libitum*. Each manipulation or experiment occurred after at least one week of acclimatisation to the housing conditions. All animals were euthanised by cervical dislocation after anaesthesia with ketamine (100mg/kg, Imalgene 1000; Merial, Lyon, France) and xylazine (10mg/kg, Rompun® 2%; Bayer, Berlin, Germany) administered intraperitoneally before tissue collection.

Study design

The animal protocol was designed to minimise pain or discomfort to the animals. Eight series of mice were used in this work. Each set was comprised of different groups of mice, and each group was formed of 5-8 mice. The first series was used to develop the cross-organ sensitisation model. Once the model was validated, a second series was used to analyse inflammatory parameters in the

colon and the bladder and to assess colonic and bladder permeabilities. We then focused on the CNS, especially at Laminas I and II of the dorsal horn at the L6-S1 segment, where pelvic EPAN form synapses with spinal neurons. Our third series assessed the neuronal activity in this model using the c-Fos expression, and inflammatory parameters were measured in the spinal cord of a fourth series. The model was then transposed on transgenic mice to assess changes in microglial cells. Finally, three different inhibitors/antagonists were used in the sixth, seventh and eighth series to better understand which pathway could be involved in the cross-sensitisation process.

Acetic acid sensitisation

An injection of AA (0.75%, 200µL) or saline (NaCl 0.9%, 200µL; Baxter, Deerfield, IL, USA) was made into the urinary bladder using ultrasound monitoring in mice under brief anaesthesia (Isoflurane: 3% in 1.5L/min of air, Iso-Vet®; Piramal Critical Care, Voorschoten, The Netherlands).

Colorectal distension and visceral sensitivity measurement

We measured visceral pain to CRD using a non-invasive method, as previously reported in mice (Larauche et al., 2010). Changes in intracolonic pressure (ICP), reflecting VMR induced by CRD (nociceptive stimulus), were used as a surrogate marker of colorectal sensitivity (Larauche et al., 2010).

An infinitely compliant distension balloon (diameter 0.7cm) was made using a polyethylene bag attached to a PE-50 catheter (Intramedics, France) drilled in its end and taped 2 cm below the pressure sensor of a miniaturised pressure transducer catheter (SPR-524 Mikro-Tip catheter; Millar Instruments, Houston, TX, USA). Polypropylene 4-0 ligatures (Prolène®; Ethicon Inc., Somerville, NJ, USA) were covered with parafilm to prevent air leaks.

On the experimental day, mice were briefly anaesthetised with Isoflurane (3% in air), and the lubricated “balloon-pressure sensor” was introduced into the colorectum, so the balloon was inserted 2 cm upstream of the anal margin into the colon. Each mouse was placed in an adjustable mouse restrainer (30 mm diameter × 90 mm length, LE5016; *In Vivo* Research Instruments, Perkin Elmer, Waltham, MA, USA) and left to rest for 30 min before the CRD procedure. The

balloon was then secured to the tail with tape and connected to an electronic barostat (Distender Series II; G&J Electronics Inc., Toronto, ON, Canada) to perform isobaric CRD. Our distension protocol consisted of a set of graded phasic distensions of 15, 30, 45, and 60 mmHg (two times each, 20 s duration, 4 min inter-stimulus interval) (Protocol Plus Deluxe; G&J Electronics, Toronto, ON, Canada). Voltage output was converted digitally using a CED digital-analogic converter (Micro 1401; Cambridge Electronic Design, Cambridge, UK) and Spike 2 software (CED, Ltd., Cambridge, UK). The pressure sensor allowed the assessment of visceral pain *via* a custom-made script that allowed signals to be extracted specifically from abdominal muscle contractions (excluding those from colonic contractions).

Colonic sensitivity was measured in awake mice at 60 minutes, three days and seven days following AA urinary bladder injections.

Measurement of bladder and colonic paracellular permeabilities

After euthanasia, bladder and distal colon samples were removed on day 7. Samples were cut along the mesenteric border. Bladder and colonic permeabilities were assessed by measuring FITC-dextran (4 kDa) fluxes in Ussing chambers with an exchange surface of 0.07 cm² (Harvard Apparatus, Holliston, MA, USA) as previously described (Beutheu et al., 2014). FITC-dextran (5 mg/mL) was loaded on the mucosal side. After three hours at 37 °C, the medium from the contralateral side (serosa) was removed and stored at -80 °C. The fluorescence level of FITC-dextran (excitation at 485 nm, emission at 535 nm) was measured in a 96-well black plate using the spectrometer Chameleon V (Hidex Co, Turku, Finland). The results were converted to concentrations of FITC-dextran (mg/mL) for analysis.

Myeloperoxidase measurement

After euthanasia, bladder and distal colon samples were removed on day 7. Colonic and vesical tissues (around 50 mg) were washed in phosphate-buffered saline (PBS) and then homogenised (50 mg/mL) in 0.5% hexadecyltrimethylammonium bromide (Sigma-Aldrich, Steinheim, Germany) with 50 mmol/L of PBS (pH 6.0). They were frozen at -80 °C and thawed at 37 °C three

times, then sonicated (Vibra Cell ultrasonic processor 75115; Bioblock Scientific, Illkirch, France) and finally centrifuged (14,000 rpm at 4 °C for 15 minutes). Myeloperoxidase was assayed in the supernatant by adding 1 mg/mL of dianisidine dihydrochloride (Sigma-Aldrich) and $5 \times 10^{-5}\%$ of hydrogen peroxide (Sigma-Aldrich). The change in optical density was measured at 450 nm. One unit of MPO activity was defined as the amount that degraded 1.0 μmol of hydrogen peroxide per minute at 25 °C, and human neutrophil MPO (Sigma-Aldrich) was used as standard, as previously described (Maaser et al., 2006, Meleine et al., 2016).

c-Fos immunofluorescence

Seven days after the intra-bladder injection of AA 0.75%, c-Fos immunohistochemistry was performed after 120 minutes of CRD at 45 mmHg (20 seconds of distension every 4 minutes for 120 minutes). Under ketamine (100 mg/kg i.p.)/xylazine (10 mg/kg) anaesthesia and upon thoracotomy, mice were perfused through a cardiac-aorta cannula with saline followed by 150 mL/mouse of ice-cold 4% paraformaldehyde and 14% saturated picric acid in a 0.1 M PBS (pH 7.2). After decapitation, the lumbo-sacral spinal cord (L6-S1) was post-fixed in the same fixative solution overnight at 4 °C, cryoprotected by immersion in 10% sucrose overnight and transferred to 30% sucrose overnight. The spinal cords were then embedded in Tissue-Tek® Optimal Cutting Temperature compound (Sakura Finetek USA, Inc., Torrance, CA, USA), snap-frozen and cut with a cryostat. Fluorescent microscopy was used to identify activated neurons. The expression of c-Fos was assessed by immunofluorescence. We applied anti-c-Fos antibody (1:2000; Calbiochem, Darmstadt, Germany) overnight at 4 °C and then incubated Cyanine-3 (Cy3)-conjugated goat anti-rabbit IgG (1:400; Fisher, Invitrogen™, Carlsbad, CA, USA) for two hours at room temperature. Pictures were taken using a fluorescence microscope (DM5500 B; Leica Microsystem Ltd., Wetzlar, Germany) at magnification x10, and the number of c-Fos immunoreactive (c-Fos-IR) cells in lamina I and II of the dorsal horn at the L6-S1 segment of the spinal cord was counted for each mouse. The average number of stained nuclei in three 20 μm thick slices for each mouse was used for analysis.

Semiquantitative PCR for the detection of TNF- α , IL-1 β and IL-10 mRNA in the spinal cord

Total ribonucleic acid (RNA) from L6-S1 spinal cord segments was extracted using TRIzol reagent (Invitrogen™, Carlsbad, CA, USA). Ribonucleic acid was purified according to the manufacturer's instructions. Total RNA was treated with DNase I (Invitrogen™) to remove any contaminating DNA. DNase I was stopped with DNase inactivation reagent (Invitrogen™) according to the manufacturer's instructions. The quality and quantity of total RNA were determined using a NanoDrop 2000 spectrophotometer (Thermo Fisher Scientific, Wilmington, MA, USA). The ratio of absorbance at 260 nm and 280 nm was used to assess the purity of RNA. A ratio of ≥ 2.0 was accepted for analysis.

After reverse transcription of 1.5 μ g total RNA into cDNA by using 200 units of SuperScript II Reverse Transcriptase (Invitrogen™), qPCR was performed using SYBR Green technology on a Bio-Rad CFX96 real time PCR system (Bio-Rad Laboratories, Marnes-la-Coquette, France). The glyceraldehyde 3-phosphate dehydrogenase (*GAPDH*) gene was chosen as the reference gene. All samples were performed in duplicate in a single 96-well reaction plate. Serially diluted cDNA samples were used as external standards. The absolute quantification of mRNA was performed by converting the sample cycle threshold (Ct) values to concentration (copies per μ L) based on standard curves. The identity and purity of the amplified products were assessed using melting curve analysis at the end of amplification. The technique was used to assay tumour necrosis factor-alpha (*TNF- α*), interleukin (IL)-1 beta (*IL-1 β*) and *IL-10* mRNA in the spinal cord. The primer sequences for the targeted mouse genes are presented in Addendum 6. Supplementary data for Article 6 (Supplementary Table 6.1).

Analysis of microglial cells

Green fluorescent protein on the fractalkine receptor-positive (CX3CR1^{gfp+}) transgenic mice were perfused as described for c-Fos immunofluorescence, and the dorsal horn of L6-S1 spinal cord was embedded in Tissue-Tek® optimal cutting temperature compound, snap-frozen and cut with a cryostat. Pictures were then taken with the Leica photonic microscope used for c-Fos experiments at magnification x10, and the number of microglial cells

expressing microglia green fluorescent protein in Laminas I and II of L6-S1 dorsal spinal cord was counted using NIH ImageJ software (version 2.0.0-rc-43/1.51u) (Rasband, 1997-2020). The average number of stained nuclei per field in three 20 μm thick slices for each mouse was used for statistics.

Pharmacologic studies

Minocycline (2.5 mg/mL; 1.25 mg/kg; Sigma-Aldrich), a microglial blocker, CP 99994 (15 mg/mL; 7.5 mg/kg; Sigma-Aldrich), a NK1R antagonist, SB203580 (5 mg/mL; 2.5 mg/kg; Calbiochem, Merck, EMD Millipore Corp., Billerica, MA, USA), a mitogen-activated protein kinase (MAPK)-p38 blocker, or saline were injected in the ICV region using a Hamilton syringe (Neuros™, Gastight, 1705, 33 gauge; Dutscher, Bernolsheim, France) one hour before injecting AA (0.75%) into the bladder. Intrathecal injections of minocycline at the L6-S1 level of the spinal cord were also performed to demonstrate that microglial activation occurred at that level.

Western blot analysis

After euthanasia, the L6-S1 segment of the mice spinal cord was removed on ice and quickly frozen in liquid nitrogen. After thawing on ice, the spinal cord samples were homogenised at 4 °C in a lysis buffer (100 μL of buffer A X2, 2 μL of 100 mM dithiothreitol, 50 μL of 1% NP40, 1 μL of 1X P8340 protease inhibitors, 2 μL of 1X P2850 phosphatase inhibitors and 200 mL of H_2O). Samples were displayed on ice for 15 min, then centrifuged at 12,000 x g for 15 min at 4 °C. The protein-containing supernatant was collected and stored at -80 °C until analysis. The proteins (25 μg) were loaded on a 4-20% gradient polyacrylamide gel (Bio-Rad), and transferred onto a nitro-cellulose membrane (GE Healthcare, Orsay, France). Membranes were then blocked for one hour at room temperature with 5% (w/v%) non-fat dry milk in Tris-buffered saline containing 0.05% Tween® 20 (Sigma-Aldrich) (TBS-T). An overnight incubation at 4 °C was then performed with primary antibodies: anti-P-p38 (1:500; Cell Signaling Technology®, Leiden, The Netherlands; P/N 4511) or anti-NK1R (1:200; Atlas Antibodies, Bromma, Sweden; P/N HPA074573) from rabbit or anti-GAPDH (1:5000; Santa Cruz Biotechnology, Tebu-Bio, Le Perray en Yvelines, France) from goat. All antibodies were diluted in

a blocking solution. After three washes, a one-hour incubation was performed with a peroxidase-conjugated IgG secondary antibody from goat anti-rabbit or from rabbit anti-goat (1:5000; Santa Cruz Biotechnology, Tebu-Bio, Le Perray en Yvelines, France). After three additional washes, immunocomplexes were revealed using the ECL detection system (GE Healthcare Life Sciences, LittleChalfont, UK). Proteins were quantified by densitometry using ImageScanner III and ImageQuant TL software (GE Healthcare Life Sciences), and standardised against the intensity of GAPDH.

Statistics

The data were expressed as means $\pm$ standard error of the mean. Quantitative data were compared between groups using an unpaired t-test, with Welch's correction in case of unequal variances. Comparisons of multiple groups were performed using one-way analysis of variance (Kruskal-Wallis test) with post-hoc analysis (Dunn's multiple comparison post-test to compare all pairs of columns to each other or Dunnett's post-test to compare all pairs of columns to controls) to assess the difference among the groups, and two-way analysis of variance with post-hoc analysis (Bonferroni's correction) was used to assess groups with repeated measures. Individual data for visceral sensitivity in mice, especially the kinetics of VMR to increasing CRD, was visually assessed for each experimental group separately; tracings of animals with aberrant or outlier responses to distensions were excluded from the analysis. A p-value < 0.05 was considered statistically significant. All statistical analyses were performed using GraphPad Prism version 9.3.1 for Windows (GraphPad Software Inc., San Diego, CA, USA, www.graphpad.com).

10.6. Results

Development and validation of a mouse model of chronic bladder-colon cross-sensitisation

Based on our previous rat study (Langlois et al., 2017), we tested the IV administration of a 0.75% AA solution in mice. A single IV injection of 0.75% AA under ultrasound monitoring induced an increase of the colonic nociceptive

response during CRD at 30 mmHg ($p < 0.05$), 45 mmHg ($p < 0.05$) and 60 mmHg ($p < 0.001$) one hour after injection (Figure 10.1). An increased colonic nociceptive response during CRD was still observed at 60 mmHg ($p < 0.05$) on the seventh day in the AA group compared to the control group (Figure 10.1), confirming that colonic hypersensitivity persists up to seven days after the IV injection in our model. Further experiments were therefore designed to understand the mechanisms of the chronicization of cross-sensitisation in this model. No serious adverse events occurred during the experiments.

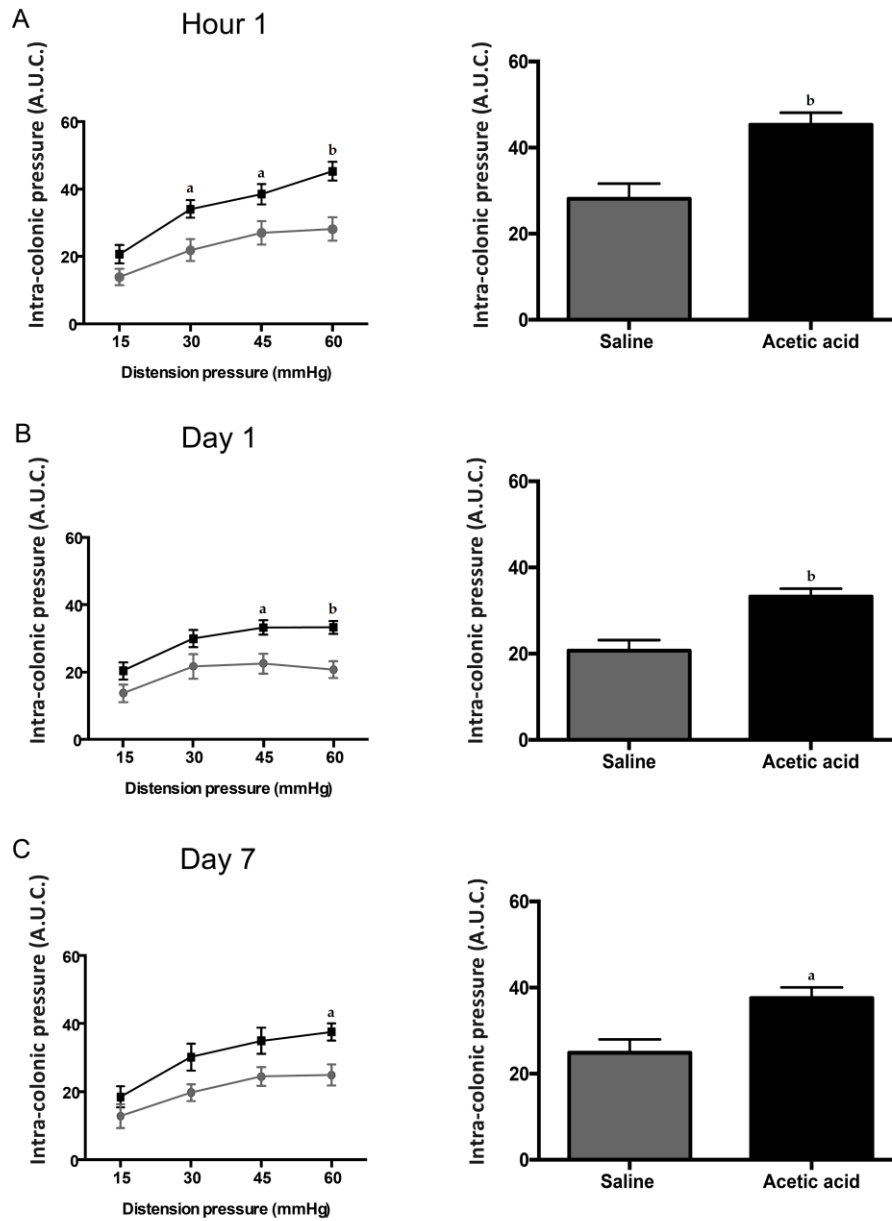


Figure 10.1. Assessment of visceromotor response to colorectal distensions. A-C: Changes in intracolonic pressure in response to isobaric colorectal distensions (15, 30, 45 and 60 mmHg) after intravesical injections of acetic acid (0.75%) vs

saline (NaCl 0.9%) in mice at 1 hour (A), 1 day (B) and 7 days (C) after injections, with details of the comparison at 60 mmHg of distension on the right. $n = 8$ mice per group.

^a $p < 0.05$ and ^b $p < 0.001$. Variability in the results is represented by the standard error of the mean (area under the curve $\pm$ standard error of the mean).

A.U.C.: area under the curve.

Permeability and inflammatory parameters of bladder and colon

No differences were found at Day 7 in either bladder or colon permeabilities or MPO activities between animals treated with AA or saline intravesically (Figure 10.2).

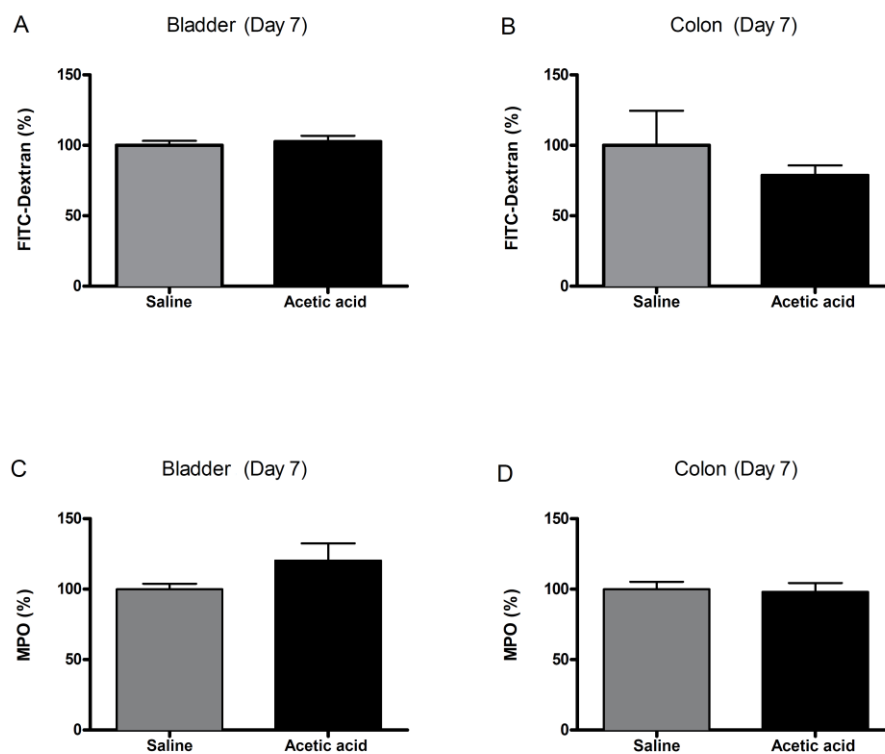


Figure 10.2. Bladder and colorectal permeabilities and inflammation.

A-D: Urinary bladder (A) and colorectal (B) permeabilities assessed by fluorescein isothiocyanate (FITC)-dextran, and urinary bladder (C) and colon (D) inflammatory levels assessed by myeloperoxidase (MPO) activities. They were not different between mice with intravesical injections of saline (NaCl 0.9%) or acetic acid (0.75%) at day 7. n = 4-5 mice per group.

Results of mice treated by intravesical injections of acetic acid were normalised to those of mice treated with saline. Variability in the results is represented by the standard error of the mean.

Neural activation in the dorsal horn of the spinal cord L6-S1

In the absence of CRD, the number of c-Fos immunoreactive cells in lamina I and II of the L6-S1 level of the dorsal horn was 6.5 ± 0.7 per slice in mice treated with saline. The CRD performed on the seventh day in these mice treated with saline increased the number of c-Fos immunoreactive cells to 12.4 ± 1.3 ($p < 0.05$). In mice treated with 0.75% AA, the number of c-Fos immunoreactive cells was 12.9 ± 1.3 in the absence of CRD and increased to 23.2 ± 1.5 ($p < 0.05$ vs all other groups) after CRD (Figure 10.3).

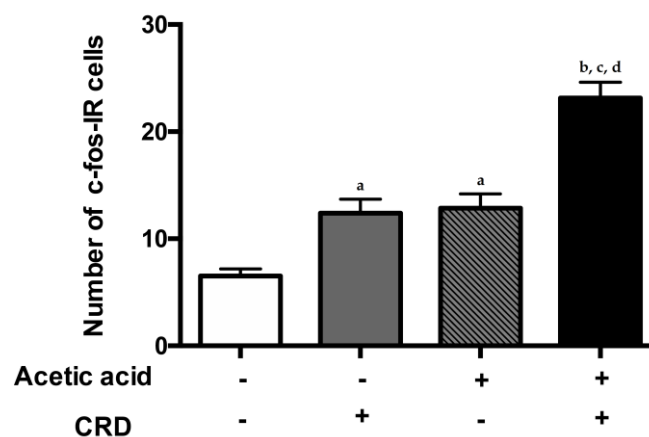


Figure 10.3. Quantification of c-Fos immunoreactive cells.

Quantification of c-Fos immunoreactive (IR) cells in lamina I and II of the dorsal horn per slice of the L6-S1 spinal cord on day 7 after intravesical injection of saline (NaCl 0.9%) or acetic acid 0.75%, with or without prior colorectal distensions (CRD) at 45 mmHg for 120 min (n = 6-7 mice per group).

^a p < 0.05 and ^b p < 0.0001 (compared to mice treated with saline and no prior CRD); ^c p < 0.001 (compared to mice treated with saline and prior CRD); ^d p < 0.01 (compared to mice treated with acetic acid and no prior CRD). Results are expressed as the mean $\pm$ standard error of the mean.

Implication of central microglia from the dorsal horn of the spinal cord L6-S1 in bladder-colon cross-sensitisation

The number of microglial cells has been observed in a transgenic mouse model which specifically expresses green fluorescent protein associated with the fractalkine receptor (Figure 10.4A and Figure 10.4B). Seven days after injection of a 0.75% AA solution into the bladder, the number of microglial cells increased compared to mice injected with saline (113.4 ± 13.0 vs 102.9 ± 11.2 per field, respectively, $p < 0.05$) (Figure 10.4C).

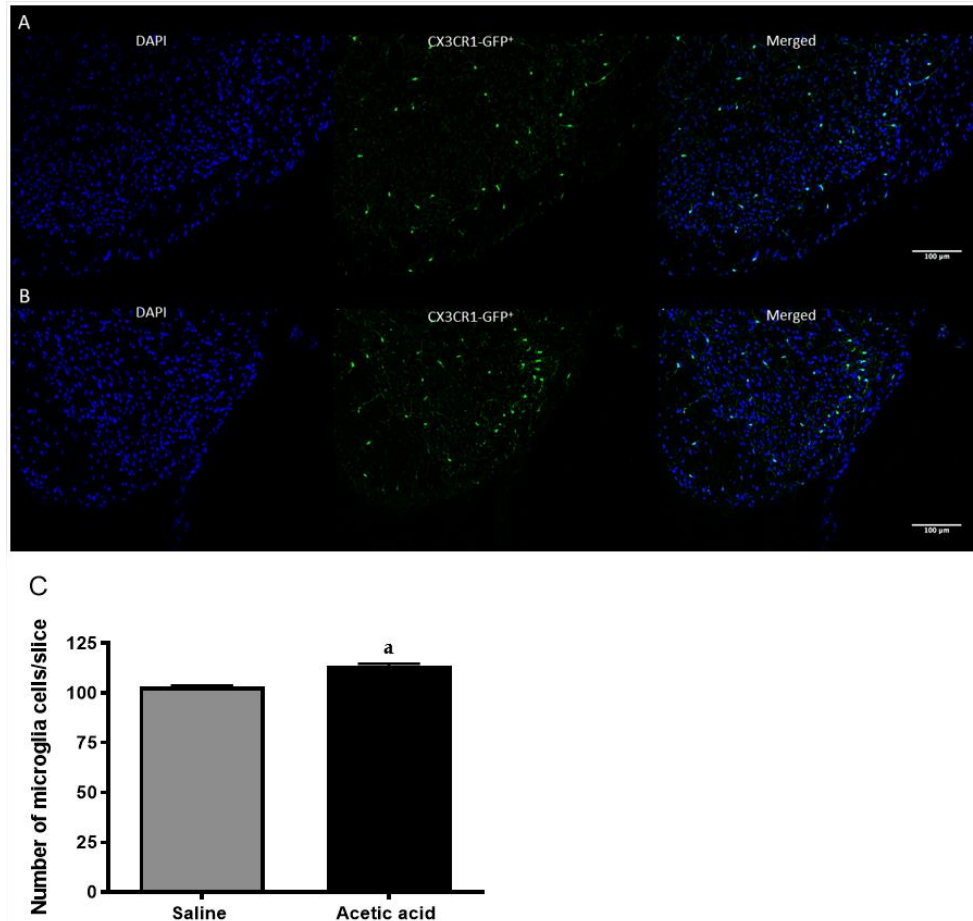


Figure 10.4. Number of microglial cells in the spinal cord.

A and B: Microglial cells in the dorsal horn of the L6-S1 level of the spinal cord were stained green [green fluorescent protein on the fractalkine receptor-positive ($CX3CR1^{GFP+}$) mice], while nuclei appear in blue (DAPI) at day 7 after intravesical injections of saline (NaCl 0.9%) (A) or acetic acid 0.75% (B); C: The number of microglial cells per field was compared between the two groups using a Mann-Whitney bilateral test ($n = 5$ per group, average of 23 slices analysed per mouse).

^a $p < 0.05$. Results are expressed as the mean $\pm$ standard error of the mean.

DAPI: 4',6-diamidino-2-phenylindole.

We administered minocycline, a microglial inhibitor, at the central level one hour before the IV injection of AA or saline to demonstrate the involvement

of microglial cells. Both IT and ICV injections of minocycline prevented the development of cross-sensitisation induced by IV administration of AA (Figure 10.5A and Figure 10.5B). Intracerebroventricular injections were favoured for the following experiments because they are less traumatic and cause less stress to the animals.

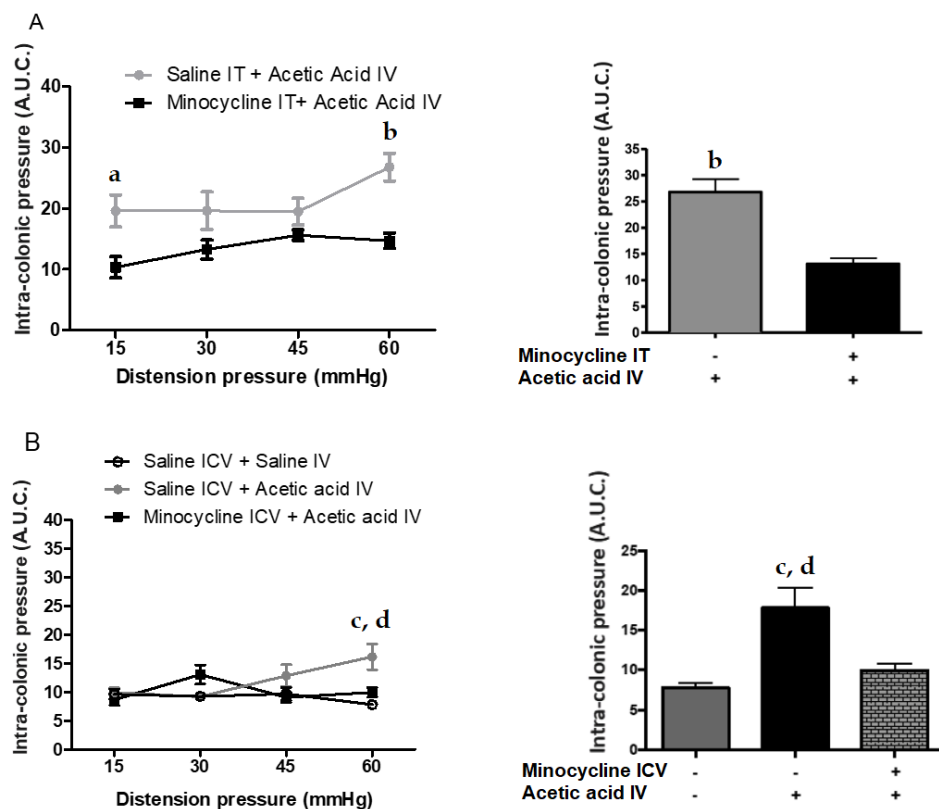


Figure 10.5. Effect of minocycline injection at the central level on visceral sensitivity.

A and B: Changes in intracolonic pressure in response to isobaric colorectal distensions (15, 30, 45 and 60 mmHg) intrathecal (IT) injections of saline (NaCl 0.9%) (A) or minocycline (1.25 mg/kg) prior to intravesical (IV) injections of acetic acid 0.75% and after intracerebroventricular (ICV) injections of saline or minocycline (1.25 mg/kg) (B) prior to IV injections of saline or acetic acid 0.75% in

mice at day 7, both with details of the comparison at 60 mmHg of distension on the right. $n = 6-8$ mice per group.

^a $p < 0.05$ and ^b $p < 0.001$ (compared to the minocycline IT + acetic acid IV group); ^c $p < 0.0001$ (compared to the saline ICV + saline IV group); ^d $p < 0.05$ (compared to the minocycline ICV + acetic acid IV group). Variability in the results is represented by the standard error of the mean (area under the curve $\pm$ standard error of the mean).

A.U.C.: area under the curve.

Involvement of central NK1R in bladder-colon cross-sensitisation

The ICV injection of CP 99994, a NK1R antagonist, one hour before the IV injection of AA, prevented the development of bladder-colon cross-sensitisation compared to mice treated intracerebroventricularly by saline (Figure 10.6A). The IV administration of AA increased the phosphorylation of MAPK-p38, a microglial protein involved in chronic pain generation (Jin et al., 2003), compared to mice injected intravesically with saline, but the ICV injection of CP 99994 prevented this phosphorylation, suggesting that microglial activation depends on the activation of NK1R (Figure 10.6B).

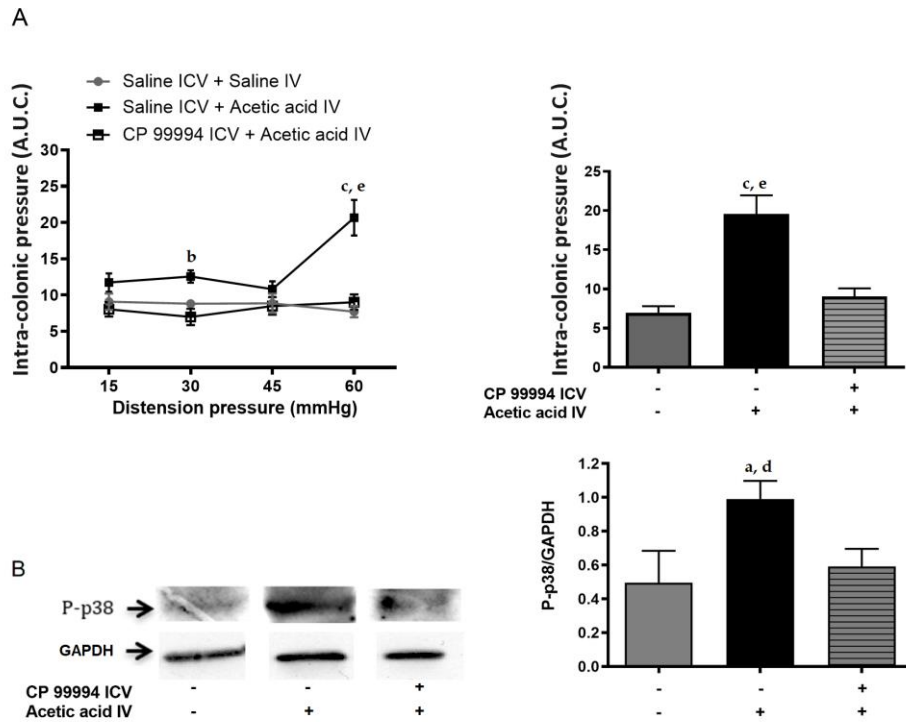


Figure 10.6. Effect of CP 99994 injection at the central level on visceral sensitivity and the expression of phosphorylated MAPK-p38.

A: Changes in intracolonic pressure in response to isobaric colorectal distensions (15, 30, 45 and 60 mmHg) after intracerebroventricular (ICV) injections of saline (NaCl 0.9%) or CP 99994 (7.5 mg/kg) prior to intravesical (IV) injection of saline or acetic acid 0.75% in mice at day 7, with details of the comparison at 60 mmHg of distension on the right. $n = 8$ mice per group; **B:** Expression of phosphorylated MAPK-p38 (P-p38) at the L6-S1 level of the spinal cord, with quantitative analysis (ratio to the reference protein GAPDH) on the right. Samples were run on separate gels and compiled for the figure. $n = 5-8$ mice per group.

^a $p < 0.05$, ^b $p < 0.01$ and ^c $p < 0.001$ (compared to the saline ICV + saline IV group);

^d $p < 0.05$ and ^e $p < 0.001$ (compared to the CP 99994 ICV + acetic acid IV group).

Variability in the results is represented by the standard error of the mean (area under the curve $\pm$ standard error of the mean).

A.U.C.: area under the curve, GAPDH: glyceraldehyde 3-phosphate dehydrogenase, MAPK: mitogen-activated protein kinases.

The ICV injection of SB203580, a MAPK-p38 inhibitor, one hour before the IV injection of AA prevented the occurrence of bladder-colon cross-sensitisation (Figure 10.7A). The IV administration of AA induced an increase in NK1R expression in the posterior horn of the L6-S1 level of the spinal cord compared to the administration of saline (Figure 10.7B). Acetic acid-induced spinal overexpression of NK1R was blocked by prior ICV administration of SB203580 (Figure 10.7B), suggesting that the MAPK-p38 pathway is involved in the development of bladder-colon cross-sensitisation.

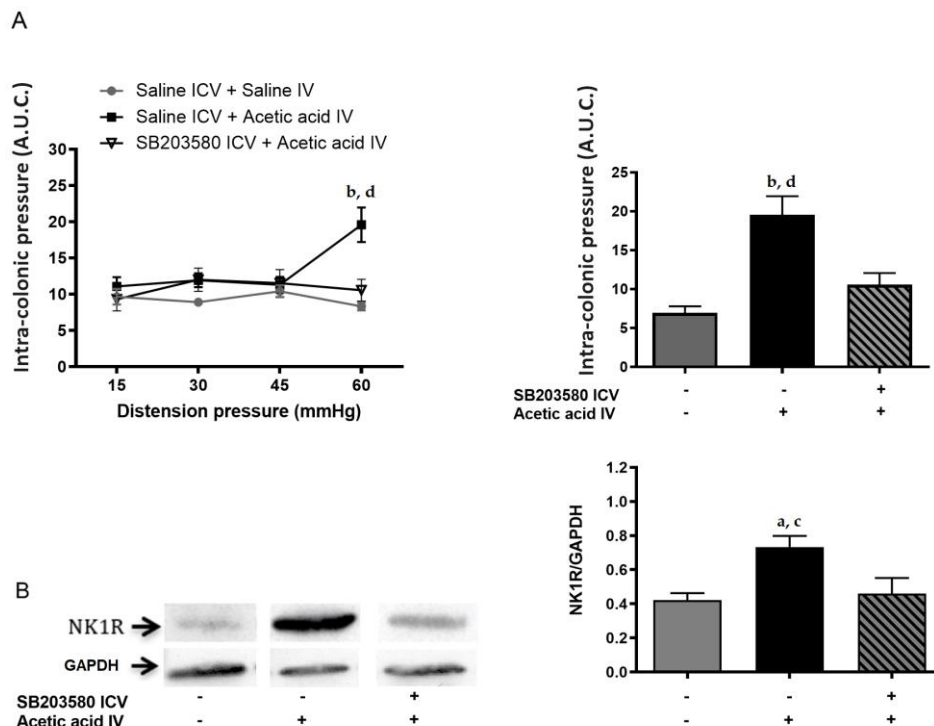


Figure 10.7. Effect of SB203580 injection at the central level on visceral sensitivity and the expression of NK1 receptors.

A: Changes in intracolonic pressure in response to isobaric colorectal distensions (15, 30, 45 and 60 mmHg) after intracerebroventricular (ICV) injections of saline (NaCl 0.9%) or SB203580 (2.5 mg/kg) prior to intravesical (IV) injection of saline or acetic acid 0.75% in mice at day 7, with details of the comparison at 60 mmHg of

distension on the right. n = 8 mice per group; B: Expression of NK1R at the L6-S1 level of the spinal cord, with quantitative analysis (ratio to the reference protein GAPDH) on the right. Samples were run on separate gels and compiled for the figure. n = 5-8 mice per group.

^a p < 0.05 and ^b p < 0.001 (compared to the saline ICV + saline IV group); ^c p < 0.05 and ^d p < 0.01 (compared to the SB203580 ICV + acetic acid IV group). Variability in the results is represented by the standard error of the mean (area under the curve $\pm$ standard error of the mean).

A.U.C.: area under the curve, GAPDH: glyceraldehyde 3-phosphate dehydrogenase, kDa: kilodalton.

Assessment of the expression of spinal pro- and anti-inflammatory transcripts

Expression levels of IL-1 β , TNF- α and IL-10 mRNA did not differ between control and AA groups (p = 0.22, 0.47 and 0.19, respectively) (Figure 10.8).

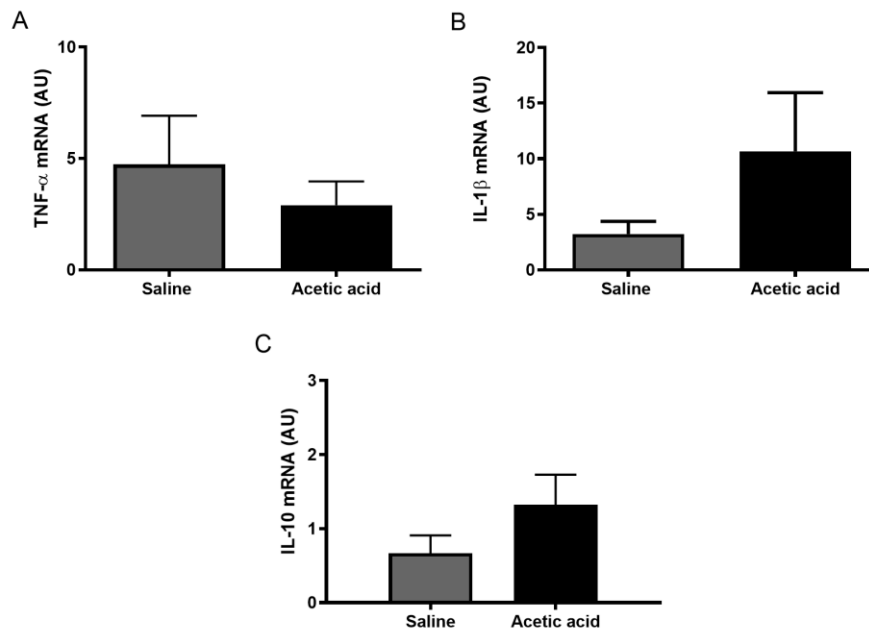


Figure 10.8. Expression of inflammatory cytokines in the spinal cord.
A-C: Expression levels of TNF- α (A), IL-1 β (B) and IL-10 (C) mRNA in the L6-S1 level of the spinal cord on day 7 were not different between mice with intravesical injections of acetic acid 0.75% or saline (NaCl 0.9%) on day 7. $n = 7$ per group. Results are expressed as the mean $\pm$ standard error of the mean. AU: arbitrary unit.

10.7. Discussion

A mouse model of bladder to colon cross-sensitisation with persistent visceral hypersensitivity in the colorectum has not been developed until now to our knowledge. Our study showed that pelvic visceral cross-sensitisation involves central sensitisation with microglial modulation following a peripheral inflammatory event and is mediated by the NK1 and MAPK-p38 pathways.

The pathophysiology of colon-bladder cross-sensitisation is complex and probably involves both peripheral and central mechanisms including: the

sensitisation of sensory nerve terminals in both organs; cross-sensitisation of adjacent sensory EPAN within DRG (involving SGCs and macrophages); axon reflexes *via* primary sensory afferent neurons with a dichotomising axon explaining neurogenic inflammation if there is a convergence of sensory information from distinct organs to a single neuron and antidromic release of inflammatory mediators in the unaffected organ (pre-spinal convergence); the sensitisation of second order spinal neurons in which there is a convergence of inputs from both colon and bladder, involving spinal interneurons (convergence-projection theory or dorsal root reflex); and supraspinal mechanisms (modified central processing of visceral stimuli in the amygdala, etc.) (Brumovsky and Gebhart, 2010). Our work adds to the current understanding that central sensitisation in the spinal cord involves microglial modulation and is mediated by NK1 and MAPK-p38 pathways.

It is already known that an increase in proinflammatory factors within the bladder tissue can sensitise the colon (Malykhina, 2007, Brumovsky et al., 2009, Furuta et al., 2014). Several mechanisms have been proposed to explain this inter-organ sensitisation. These mechanisms include the increased mechanical sensitivity of visceral muscle afferents, a higher proportion of chemo-sensitive visceral afferents (Brumovsky et al., 2009), brainstem neurons integrating somato-visceral messages after bladder irritation (Kaddumi and Hubscher, 2007), and central sensitisation resulting from stressful life events (Mayer, 2011).

In our study, we used a mouse model of colonic visceral hypersensitivity induced by cross-organ sensitisation to demonstrate that microglia plays a central role in the development of this hypersensitivity. Indeed, we showed that the ICV injection of minocycline, which is known to be an inhibitor of microglial cells, blocks the cross-sensitisation process. It has already been shown that minocycline also induces a decrease in neuronal excitability by preventing phosphorylation of the ERK protein and MAPK, which are expressed in the spinal cord (Cho et al., 2012). The analgesic effect of minocycline is mediated by its action in both microglial activation and neuronal activation. Microglial cells have already been shown to be recruited during colonic sensitisation induced by chronic stress in rats (Bradesi et al., 2009), but our study is the first to identify the crucial role of microglia in bladder to colon cross-sensitisation and in a mouse model.

We showed that the role of microglia in the development of cross-sensitisation from the bladder to the colon is mediated by the tachykininergic

pathway, particularly involving NK1R. This receptor activates, directly or indirectly, the MAPK-p38 protein *via* its phosphorylation. Several studies have confirmed that MAPK-p38 is expressed only by microglial cells (Jin et al., 2003, Ji and Suter, 2007, Ji et al., 2013). Its involvement in the course of chronic stress-induced colonic sensitisation has already been demonstrated in rats (Bradesi et al., 2009). Another study suggested that the activation of microglial MAPK-p38 protein at the ventromedial nucleus of the spinal cord (rostral ventromedial medulla) was responsible for utero-colonic cross-sensitisation in an acute model (Chen et al., 2015). In our work, we found that visceral hypersensitivity induced by chronic stress was associated with the phosphorylation of MAPK-p38 at the microglial cell level in mice and that this effect was inhibited by the ICV injection of a MAPK-p38 inhibitor (SB203580).

Bradesi et al. also showed that the fractalkine receptor potentiates the development of visceral hypersensitivity *via* a chemokine function on NK1R (Bradesi et al., 2009). The activation of MAPK-p38 is known to be associated with the increased synthesis and secretion of several neurotransmitters of inflammation, such as cyclooxygenase-2 (COX-2), IL-1 β , inducible NOS (iNOS), phospholipase A2 (PLA2) and prostaglandin E2 (PGE2) (Svensson et al., 2003). The mediators of inflammation involved in our model are probably different from those involved in the TNBS-induced colitis models, in which expression of IL-1 β is upregulated in the spinal cord (Majima et al., 2018) since we did not demonstrate any changes at the *TNF- α* , *IL-1 β* and *IL-10* mRNA level.

We therefore propose a mechanistic view of the molecular and cellular mechanisms underlying the development of colonic hypersensitivity by bladder-to-colon cross-sensitisation in which the inflammatory reaction following irritation of the urothelium induces the activation of EPAN, some of them co-innervating the bladder and the colon, and giving rise to axon reflexes, while others innervating the colon are activated by paracrine interactions. Convergent neurons in the DRG and the spinal cord, and those innervating the colon, secondarily sensitise the colon. Some activated EPAN relaying to other neurons in the dorsal horn of the spinal cord specifically secrete substance P, a member of the tachykinin family, which binds to NK1R, activating the MAPK-p38 by phosphorylation. This in turn could either directly or indirectly induce the synthesis of mediators involved in neuroplasticity and neuroinflammation in the spinal cord.

A mini-invasive approach that specifically targets the bladder without inducing structural lesions in neighbouring areas (especially the colon and peritoneum) is a prerequisite for cross-sensitisation. Indeed, abdominal surgery is known to induce stress, involving a hormonal stress response at the peripheral and central levels, and implicating the corticotropin releasing factor pathways (Tache and Bonaz, 2007). It can induce visceral sensitisation in the absence of signs of overt inflammation in mice (Larauche et al., 2010). Similarly, we decided to use measurements of the intra-colonic pressure as a surrogate marker of VMR induced by CRD to assess visceral sensitivity in our study. This technique was an alternative to the measurement of the electromyographic activity of the abdominal muscles (Larauche et al., 2009) and had the advantage of being minimally invasive.

When we planned our study, the available animal models for the study of bladder-bowel interactions included acute (Pezzone et al., 2005) and chronic (Bielefeldt et al., 2006, Lamb et al., 2006) colon irritation with TNBS in mice (Lamb et al., 2006) and in rats (Pezzone et al., 2005) and acute bladder irritation by cyclophosphamide, an antitumoral drug known to induce haemorrhagic cystitis in mice (Bielefeldt et al., 2006) and by infusing protamine sulphate and potassium chloride in rats (Pezzone et al., 2005). In those studies, colonic sensitivity was assessed on Day 5 after bladder irritation in mice and on the day of the irritation in rats.

The main limitation of our model is that the chronicity of the cross-organ sensitisation was considered at Day 7 following bladder irritation in mice. This period may seem short in view of clinical situations that evolve over several years. However, no other inflammatory model of cross-sensitisation from the bladder to the colon published in the literature exceeds 48 hours (Bielefeldt et al., 2006). Furthermore, stress-induced chronic colonic sensitisation models with 11 days of homotypic stress (Bradesi et al., 2009) were shown to be sufficient to induce changes in colonic tenderness and spinal microglial modulation. Our seven-day period in mice therefore seems to be long enough to attest to the chronicity of the process. Further studies with a longer longitudinal assessment of visceral sensitivity are necessary to confirm our results. Our results can only be extrapolated to males because sex-dependent differences in the responses to the sensitisation process (Yoshiyama et al., 2008, Ji et al., 2012) and microglia (Guneykaya et al., 2018) have been reported. Since pelvic neuroanatomy is

similar in other rodents and in humans, we could expect similar results in those species, which could explain in part the common overlap between BPS and IBS in the clinic.

10.8. Conclusion

In conclusion, we have developed the first model of cross-organ chronic visceral sensitisation between bladder and colon in mice. Pelvic cross-sensitisation involves central sensitisation with microglial modulation and is mediated by the NK1 receptor pathway and MAPK-p38 activation.

10.9. Concluding paragraph

Summary of the main findings

- A new model of cross-organ visceral sensitisation between the bladder and the colon has been developed in mice.
- Intravesical injections of AA induce a long-lasting colonic hypersensitivity to distension.
- Bladder-colon cross-sensitisation is mediated by neuroglial interactions, MAPK-p38 phosphorylation and the NK1R in this model.

Inferences

- A bladder-colon chronic cross-sensitisation mouse model using IV injections of AA can be used as a preclinical model of overlap between BPS and IBS.
- Microglial interactions are central in bladder-colon cross-sensitisation.

Perspectives

- Confirm the results on the longer-term.
- Assess minocyclin as a protective factor for the development of colonic hypersensitivity following urinary tract infection or prostatitis.

Dissemination

- The data presented in this chapter have been published in the *World Journal of Gastroenterology*:
Karim Atmani, Fabien Wuestenberghs, Maximilien Baron, Illona Bouleté, Charlene Guérin, Wafa Bahlouli, David Vaudry, Jean Claude do Rego, Jean-Nicolas Cornu, Anne-Marie Leroi, Moïse Coëffier, Mathieu Meleine and Guillaume Gourcerol. Bladder-colon chronic cross-sensitization involves neuro-glial pathways in male mice. *World Journal of Gastroenterology* 2022; 28 (48): 6935-6949.
<https://doi.org/10.3748/wjg.v28.i48.6935> (IF = 5.37)
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- Key messages from our work were shared on Twitter :
 - Wuestenberghs, F. [@wuefab] (2022). Karim Atmani's thesis work on a new #bladder-#colon chronic cross-sensitization model in male mice has been published in the World J Gastro. Key role of #microglia. <https://dx.doi.org/10.3748/wjg.v28.i48.6935> @U1073lab @mcoefficient76

Chapter 10

@JnCornu @Bouletellona @univrouen @normandieuniv #hypersensitivity
[Twitter] 27 December]. Available
on: <https://twitter.com/wuefab/status/1607748798872264707> (Consulted on:
December 27, 2022).

Impact of the research

- This paper has been cited 0 time [ consulted on March 16, 2023].
- The Altmetric score is 8 [ consulted on March 16, 2023].



Chapter 11 ARTICLE 7. DEVELOPMENT OF A CHRONIC COLON-STOMACH CROSS-SENSITISATION MODEL IN RATS

11.1. Introductory paragraph

Articulation with previous projects

Overlap between FD and IBS is frequent, as we have seen in our systematic review (see Chapter 3 Article 1). Both disorders are characterised by a post-infectious origin and the presence of visceral hypersensitivity in a subset of patients. Cross-organ visceral sensitisation has been reported between organs sharing common sensory pathways, as we have shown in the previous work (see Chapter 10 Article 6). Pathomechanisms of FD-IBS overlap remain unclear, however, and we decided to study the possibility of colon-stomach cross-sensitisation, similarly to the previous experimental work performed in the laboratory, since the stomach and proximal colon share common innervation.

What is already known?

Functional disorders of the upper and lower GI tracts frequently overlap in patients. Cross-organ visceral sensitisation has been reported between organs sharing common sensory pathways, especially between the bladder and the colon.

Research questions

- Can experimental colitis induce gastric hypersensitivity?
- If applicable, which pathway(s) are involved in the colon-stomach cross-sensitisation?

Aims

- Develop a rat model of colon-stomach cross-sensitisation.
- Investigate the mechanisms involved in the cross-sensitisation.

Methodology

- Animals: 7-weeks-old male Sprague-Dawley rats weighing 300-400g

- TNBS-induced colitis for colon to stomach sensitisation
- Gastric and colorectal sensitivity were assessed in rats sedated by phenobarbital by measuring changes in blood pressure measured at the left carotid artery during isobaric gastric and colorectal distensions.
- Tissue inflammation: MPO
- Tissue permeability: Ussing chambers
- Systemic inflammation: cytokine multiplex assay
- Inflammation at the spinal level: qPCR
- Expressions of NK1 receptors and MAPK-p38 in the spinal cord: WB
- Control group with systemic inflammation induced by intraperitoneal administration of LPS
- Pharmacological studies using IT injections of minocycline, CP 99994 or saline

My contribution

I designed the research study, I performed the research, I analysed the data, I drafted the manuscript, and I revised critically the manuscript for important intellectual content. In particular, I did all the manipulations on the animals alone but the molecular analyses were carried out jointly with the laboratory technicians Christine Bole-Feysot and Charlène Guérin (except the Ussing chambers which I carried out myself and the WB analysis of the expression of NK1R which was carried out by the laboratory technicians alone).

The progress of this work was marked by several difficulties (shortage in thiobutabarbital [Inactin®] with the need to change the barbituric to pentobarbital [Gardenal®], cessation of the experiments during two months-long periods due to COVID-19 restrictions and during antihelminthics treatment at the animal facility, endemic infection by *Syphacia muris* in the animal facility, etc.) and aborted stages of the project (iodoacetamide-induced gastritis, acetic acid-induced colitis, etc.), which are not detailed further.

11.2. Title page

Complete title

Chronic cross-organ visceral sensitisation between colon and stomach in rats

Short title

Colon-stomach cross-sensitisation

Authors' names

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11.3. Abstract

Background/Aims

Overlap between functional dyspepsia (FD) and irritable bowel syndrome (IBS) is frequent and both disorders are characterised by visceral hypersensitivity in a subset of patients. Pathomechanisms of FD-IBS overlap remain unclear. Cross-organ visceral sensitisation has been reported between organs sharing common sensory pathways. The stomach and proximal colon are both innervated by the vagus nerve, however, the possibility of colon-stomach cross-sensitisation has not been assessed in adult animal models. The aims of this study were to develop a rat model of colon-stomach cross-sensitisation and to investigate the mechanisms involved.

Methods

Colon-stomach visceral cross-sensitisation was assessed in 7-weeks-old Sprague-Dawley rats using acute TNBS-induced colitis for colon to stomach sensitisation. Gastric and colorectal sensitivity were assessed in rats sedated by phenobarbital by measuring changes in blood pressure measured at the left carotid artery during isobaric gastric and colorectal distensions. Myeloperoxidase (MPO), used as a marker of gut inflammation, was measured in the stomach and the distal colon, and permeability of both organs was measured using Ussing chambers. Systemic inflammation was assessed using a cytokine multiplex assay, while inflammation at the spinal level was assessed by qPCR. Finally, the expressions of NK1 receptors and MAPK-p38 were quantified in the spinal cord using western blot.

Key results

Gastric hypersensitivity was observed 2 and 7 days after the colonic administration of TNBS compared to saline. Colorectal hypersensitivity was observed on day 7 after colonic insult. No increased tissue permeability or inflammation was shown in the stomach and colon, and no systemic inflammation was present, 2 and 7 days post-colonic administration. The expression of phosphorylated MAPK-p38 in the spinal cord was increased at day 2 after the colonic administration of TNBS compared to saline. Gastric hypersensitivity was prevented by IT injection of minocycline, a microglial inhibitor.

Conclusions

We describe a new model of chronic cross-organ visceral sensitisation between the colon and the stomach in rats. TNBS-induced colitis induces long-lasting colorectal and gastric hypersensitivities to distension, mediated by MAPK-p38 pathway and prevented by the inhibition of microglia.

11.4. Introduction

OVERLAP BETWEEN DIFFERENT DGBI is frequently encountered in clinical practice. In particular, overlap between FD and IBS, disorders of the upper and lower GI tracts respectively, is among the most frequent: 14% of FD patients had IBS and 14% of IBS patients had FD according to modified Rome II criteria in a population-based study (Lee et al., 2009). Similarly, overlaps between DGBI and non-GI disorders have been reported. The best documented is the overlap between BPS and IBS: 40-60% of IBS patients have BPS (Mathieu, 2009) and 25-39% of BPS patients have IBS (Alagiri et al., 1997, Nickel et al., 2010). All those disorders share some pathophysiological mechanisms, especially visceral hypersensitivity in a subset of patients (at the urinary tract level for BPS (Lai et al., 2014), at the intestinal level for IBS (Naliboff et al., 1997) and at the gastric level for FD (Tack et al., 2001)). The mechanisms of overlaps are however unclear. Bidirectional cross-organ visceral sensitisation between the bladder and the colon has been shown to play a role in the overlap between BPS and IBS based on animal experiments (Pezzone et al., 2005, Langlois et al., 2017), pelvic organs sharing common sensory pathways. Increasing evidence show that spinal glia plays a role in cross-sensitisation between bladder and colon (Atmani, 2018, Qiao and Tiwari, 2020). The stomach and proximal colon are both innervated by the vagal nerve but the possibility of colon-stomach cross-sensitisation has never been assessed in animal models.

Our hypothesis was that cross-organ visceral sensitisation occurs between the stomach and the colon in the rat. Our objectives were therefore to develop a rat model of colon-stomach cross-sensitisation and to investigate the mechanisms involved in its development.

11.5. Methods

Ethical statement

Our experiments were performed in accordance with the ethical guidelines of the IASP (Zimmermann, 1983) and the European Directive 2010/63/EU on the protection of animals used for scientific purposes, and were approved by the Ethics Committee for Animal Experiments (APAFIS#11895-

2019010211383207). The ARRIVE guidelines (Kilkenny et al., 2010) were followed for the redaction of the paper.

Animals

Adult male Sprague-Dawley rats (*Rattus norvegicus*; Janvier Laboratories, Le Genest-Saint-Isle, France), aged 7 weeks old with a mean weight of 337.9g (range 294.6-388.6g) on the day of the experiment, were used. Animals were randomised by groups of 2 or 3 per cage to separate animals from different experimental groups. Animals were kept in an animal housing facility on a 12-hour day/night cycle and with controlled room temperature (22 ± 2 °C). The environment was free of specific pathogenic organisms; a sentinel rat was shown free of any pathogen, especially *Syphacia muris* and *Helicobacter spp*, and faeces from all animals were pooled and checked for the presence of *S. muris* by PCR (GM diagnostics, The Netherlands, www.qmdiagnostics.org) since pinworms are known to prevent DSS-induced colitis in mice (Taghipour et al., 2019). The animals received a standard diet (Genestil; 22.6% proteins, 5.0% fat, 4.5% fibres, 7.1% ash and nutritional additives; Altromin Spezialfutter GmbH & Co. D-32791 Lage, Germany). Drinking water and food were available *ad libitum*. Experiments began after at least one week of acclimatization to the conditions of stabling. All animals were euthanised before tissue collection by cervical dislocation after anaesthesia with phenobarbital (300 mg/kg; Gardenal® Sanofi-Aventis France, 94250 Gentilly, France) administered intraperitoneally.

Experimental protocols

Our study protocol was designed to minimize pain or discomfort to the animals. Three series of rats were used in this work. The first series was used to develop the cross-organ sensitisation model and samples were taken for analyses. This series was composed of 3 groups: controls (n = 12), TNBS-induced colitis assessed on day 2 (n = 9) and TNBS-induced colitis assessed on day 7 (n = 15). Different parameters were retrieved: age, weight, faecal pellet output 1 hour after intracolonic administration of TNBS or saline, stool consistency over time, colonic weight and length, gastric weight, and the amount of phenobarbital needed to sedate each animal (mL/g of rat body weight). Once the model was

validated, a second series was used to test different inhibitors/antagonists to gain a better understanding of which pathway could be involved in the cross-sensitisation process. This series was composed of 4 groups all assessed on day 7: controls (n = 13), TNBS-induced colitis with prior IT injection of saline (n = 18), TNBS-induced colitis with prior IT administration of minocycline (n = 8), and intraperitoneal injection of LPS (n = 10). This latter group was intended to assess the effect of systemic inflammation on the development of gastric hypersensitivity. Finally, a third series was used to assess colonic and gastric permeabilities. No blinding was used since outcome measures, carotid artery pressure modulation, are objective and not subject to change based on the beliefs of the investigators. Animals were allocated to different cages at random upon arrival at the animal facility by animal technologists. All animals in the same cages always belonged to the same group.

Chemical colitis

Twenty-five milligrams of TNBS (picrylsulfonic acid solution, #92822; Sigma-Aldrich Co., MO 63103, USA) in 50% of ethanol (total volume 250µL) was instilled into the colon 8cm upstream of the anal margin using a 1.2mm polyethylene catheter in rats under Isoflurane sedation (3% in 2.5L/min of air, Iso-Vet®, Piramal Critical Care, Voorschoten, The Netherlands) to induce colitis. The same volume of saline (NaCl 0.9%) was instilled in control rats. No post-procedural analgesia was administered. Rats were maintained in Trendelenburg manually for 2 minutes to ensure exposure of the colon by the irritants and were then placed in a slight Trendelenburg for their awakening phase.

Assessment of visceral sensitivity

On experimental day, rats were hypnotised with phenobarbital (300 mg/kg; Gardenal®, Sanofi-Aventis France, 94250 Gentilly, France) administered intraperitoneally upon disappearance of pain reflex. The rats had been fasting for at least 6 hours (overnight fast). The cervical skin and upper abdominal incision areas were shaved and then disinfected with ethanol 30%. A 1cm-long left lateral cervical incision was performed after local subcutaneous anaesthesia with lidocaine (Xylocaine® 2%, 0.1mL, Aspen Pharmacare, Durban, South Africa) to

access the left carotid artery. The carotid artery was carefully isolated from the vagus nerve, without ligating or damaging it. After clamping the proximal part of the carotid artery and ligating its distal part using violet braided synthetic absorbable suture (Vicryl™ 3-0, Ligapak™; Ethicon, LLC. Johnson & Johnson International, reference JV1205), a 1.2mm polyethylene perfused catheter (NaCl 0.9% with heparin 0.5%) was inserted in the left carotid artery and secured in its lumen using a knot (Vicryl™ 3-0). This catheter was connected to a miniaturised pressure transducer catheter (SPR-524 Mikro-Tip catheter; Millar Instruments, Houston, TX, USA) to register pressure variations. Then, a 1cm-long upper mid-abdominal incision was performed after local subcutaneous anaesthesia with lidocaine (Xylocaine® 2%, 0.1mL) to access the stomach. After incising the proximal stomach (1-2mm), any residual gastric content was removed using a syringe for gentle successive instillations and re-aspirations of water at room temperature. A 3 cm-long balloon was then placed in the stomach and its position was secured by a knot around the catheter using non-absorbable braided silk (Ethicon® Perma-Hand™ seide 4-0; Ethicon, LLC. Johnson & Johnson International, reference F736). The infinitely compliant distension balloon was made using a polyethylene bag attached to a 1.2mm polyethylene catheter attached to it by polypropylene ligatures (Prolène® 4-0; Ethicon Inc., Somerville, NJ, USA), which were covered with parafilm to prevent any air leak. The abdominal incision was then sutured using the same non-absorbable braided silk (Ethicon® Perma-Hand™ seide 4-0). The catheter was then connected to an electronic barostat designed for laboratory animals (Distender Series II™, G&J Electronics Inc., Toronto, ON, Canada) to perform isobaric distensions. Our distension protocol consisted of a set of graded phasic distensions of 10, 20, 30, 40 and 60 mmHg, repeated twice each, lasting 20 seconds, and separated by 4 minutes of rest, using Protocol Plus Deluxe software (version 6.7R, 2004; G&J Electronics, Toronto, Canada). Output signals were amplified, converted digitally using CED digital-analogic converter (Micro 1401, Cambridge Electronic Design, Cambridge, UK) and recorded using Spike 2 software (CED, Ltd., Cambridge, UK). Once the distension protocol at the stomach level was completed, a 2 cm-long infinitely compliant balloon, made in the same way as the one used in the stomach, was inserted through the anus, using K-Y® lubricating jelly (Johnson & Johnson International) 2 cm upstream of the anal margin into the colorectum and was then secured to the tail with tape and connected to the barostat to perform isobaric CRD. The intragastric balloon

was left in place but disconnected from the barostat during the CRD. Our distension protocol in the colorectum consisted of a set of graded phasic distensions of 20, 40, 60 and 80 mmHg, repeated twice each, lasting 20 seconds, and separated by 4 minutes of rest. Once the distension protocol was finished, rats were euthanised and tissue samples were collected. A necropsy was performed to guarantee the absence of signs of recovering from gastric inflammation (adhesions, etc.) or peritonitis due to covered colonic perforation; otherwise, rats were excluded from analysis. Recorded pressure signals were processed by applying the following parameters: DC remove (time constant = 20 seconds), smooth (time constant = 5 seconds), no rectification. Variations in blood pressure, a pseudo-affective reflex in the rat, were used as a surrogate of VMR to visceral pain in our animals. These variations were quantified by measuring the area under the curve (AUC) of the processed signal during the distension timeframe of 20 seconds for every distension (*modulus* function), as previously described (Meleine et al., 2020).

Pharmacologic studies

Minocycline hydrochloride (2.5 mg/mL, 1.25 mg/kg (Hua et al., 2005, Mei et al., 2011, Deng et al., 2019); #M9511; Sigma-Aldrich Co., MO 63103, USA), a microglial blocker, or saline have been injected intrathecally at the L5-L6 level of the spinal cord, two minutes before injecting TNBS (25mg) into the colon. Transcutaneous puncture in the IT space was made using a 26G Terumo® Agani™ needle (Zhejiang Kindly Medical Devices Co., Ltd. 325025 Wenzhou, PRC) to deliver 50µL of reagent flushed by 50µL of saline (Mestre et al., 1994). The IT positioning of the needle was confirmed by the visualization of a tail movement during injection. Lipopolysaccharide from *Escherichia coli* (serotype 0111:B4; L3024) were administered intraperitoneally (1mg/kg; Sigma-Aldrich Co., MO 63103, USA) seven days prior to sensitivity assessment (Coelho et al., 2000).

Assessment of tissue inflammation

The MPO activity was determined. Stomach and distal colon samples were removed after euthanasia, were washed in phosphate-buffered saline (PBS) and quickly frozen in liquid nitrogen. All samples were then kept at -80°C until assays.

Colonic and gastric tissues (weighted maximum 50 mg) were homogenised (50mg/mL) in hexadecyltrimethylammonium bromide (HTAB; Sigma-Aldrich Co., MO 63103, USA) with phosphate buffer (150mg of HTAB /30mL of phosphate buffer at pH 6). They were sonicated (Vibra Cell ultrasonic processor, model 75115, with CV33 probe; amplitude 40%; Bioblock Scientific, Illkirch, France), then frozen at -80 °C and thawed at 37 °C alternatively three times, and finally centrifuged (15,000 g at 4 °C for 15 minutes) to keep the supernatant. Myeloperoxidase was assayed in the supernatant by adding a reaction buffer prepared with 6.8mL of phosphate buffer, 6.4mL of O-dianisidine dihydrochloride (ODHC, 1mg/mL; Sigma-Aldrich Co., MO 63103, USA) and 9.5mL of hydrogen peroxide (H₂O₂) at 5 × 10⁻⁴ % (Sigma-Aldrich Co., MO 63103, USA). The change in optical density was measured at 450 nm using an absorbance microplate reader (infinite F50; Tecan, Mannedorf, Switzerland). One unit of MPO activity was defined as the amount that degraded 1.0 µmol of H₂O₂ per minute at 25 °C and is expressed as unit/mL of tissue (1mL of buffer was used for 50mg of tissue and 50µL of this preparation was used for the assays). Human neutrophil MPO (reference M6908, Sigma-Aldrich Co., MO 63103, USA) was used as a standard and the activity was extrapolated against the standard range, as previously described (Maaser et al., 2006, Meleine et al., 2016).

Indirect colonic inflammatory markers were also assessed: macroscopic stool patterns and water content of the faeces during the days following the sensitisation, macroscopic evaluation of the colon following euthanasia by using a validated scoring system, the Macroscopic Score (MaS) (Ferreira-Duarte et al., 2021), and change in weight and length of the colon.

Cytokine measurements on plasma

Arterial blood was taken in heparinised tubes (BD Vacutainer®, BD-Plymouth. PL6 7BP. UK) and kept on ice until centrifuged (4,000 g during 20 minutes at 4°C) for plasma extraction. All samples were then kept at -80 °C until assays. Plasma samples were assayed for measurement of *IL-1β/IL-1F2*, *IL-6*, *IL-10* and *TNF-α* using magnetic bead-based multiplex assay for the Luminex® platform (LXSARM; R&D Systems, Inc. MN 55413, USA) with the BIO-RAD Bio-Plex™ 200 system with HTF (high-throughput fluidics; Bio-Rad, Hercules, CA, USA), according

to standard instructions except that samples were not diluted before processing. Results out of range and below the lower limit were considered as null.

Semi-quantitative reverse transcription polymerase chain reaction (sqRT-qPCR) for the detection of TNF- α , IL-1 β and IL-10 messenger RNA (mRNA) in the spinal cord

After euthanasia, the T8-T9 segment of the spinal cord was removed and quickly frozen in liquid nitrogen. Total RNA from T8-T9 spinal cord segments was extracted using TRIzol[®] reagent (Invitrogen[™], Carlsbad, CA, USA). Ribonucleic acid was purified according to the manufacturer's instructions: total RNA was treated with DNase I (Invitrogen[™], Carlsbad, CA, USA) to remove any contaminating DNA, then DNase I was stopped with DNase inactivation reagent (Invitrogen[™], Carlsbad, CA, USA). The quality and quantity of total RNA were determined using a NanoDrop 2000 spectrophotometer (Thermo Fisher Scientific, Wilmington, MA, USA). The ratio of absorbance at 260 nm and 280 nm was used to assess the purity of RNA. A ratio of ≥ 1.8 was accepted for analysis (Bustin et al., 2009). Then, 1.0 μ g of total RNA was reverse-transcribed into complementary DNA (cDNA) by using 200 units of Moloney Murine Leukemia Virus (M-MLV) Reverse Transcriptase kit (#28025013; Invitrogen[™] by Thermo Fisher Scientific, Inc.; Life Technologies Corporation, OR 97402, USA). Quantitative PCR (qPCR) was then performed in duplicate for each sample using SYBR[®] Green fluorescent dye (iQ[™] SYBR[®] Green Supermix, reference 172-5121; Bio-Rad Laboratories, Inc., Marnes-la-Coquette, France) on a real-time PCR detection system (Bio-Rad CFX96[™]; Bio-Rad Laboratories, Marnes-la-Coquette, France). The quantity of DNA is measured using this fluorescent dye (increasing fluorescent signal is proportional to the number of amplicons generated). The threshold cycle (Ct) is the cycle number at which the signal crosses the level of signal reflecting a significant increase over the baseline signal. The GAPDH and ribosomal protein S18 (*RPS18*) genes were chosen as reference genes. The amount of PCR products after a fixed number of PCR cycles made it possible to deduce the amount of specific messenger RNA (mRNA). Concentration values were inferred from Ct values based on standard curves, allowing to estimate the quantity of starting material in a sample. Results were expressed as the ratio between starting quantities (SQ) of the target genes to the housekeeping genes; comparisons between TNBS and control rats showed

upregulation, downregulation or absence of change in the expression of those genes of interest. The same technique was used to assess the levels of transcription of *TNF- α* , *IL-1 β* and *IL-10* genes in the spinal cord. The primer sequences of the rat genes of interests are shown in Table 11.1.

Table 11.1. Primer sequences of genes of interest for the RT-qPCR.

Gene of interest	Forward primer sequence	Reverse primer sequence	Tm (°C)
GAPDH	5' CATCACTGCCACTCAGAAGA 3'	5' AAGTCACAGGAGACAACCT 3'	60
IL-1β	5' GGGATGATGACGACCTGC 3'	5' ATACCACTTGTGGCTTATGTT 3'	58
IL-10	5' CAGTCAGCCAGACCCACA 3'	5' GGCAACCCAAGTAACCCT 3'	58
RPS18	5' TGCAGTACTCAACACCAACA 3'	5' TTCCTCAACACCACATGAGC 3'	60
TNF-α	5' GTCGTAGCAAACCAACAAGC 3'	5' GGTATGAAGTGGCAAATCGG 3'	60
GAPDH: glyceraldehyde 3-phosphate dehydrogenase, IL: interleukin, RPS18: ribosomal protein S18, RT-qPCR: reverse transcription quantitative polymerase chain reaction, Tm: melting temperature, TNF: tumour necrosis factor.			

Western blot analysis

We only had one spinal cord sample per animal and both the RNA and proteins were therefore extracted from the same samples using TRIzol® extraction protocol as described above. The proteins were then taken up by home-made Laemmli sample buffer 2x concentrate. The protein-containing supernatant was collected and stored at -80 °C until analysis. After thawing, the proteins (15 μ L) were loaded on a 4-20% gradient polyacrylamide gel (Bio-Rad, Marnes la Coquette, France) and transferred onto a nitro-cellulose membrane (GE Healthcare, Orsay, France). Membranes were then blocked for one hour at room temperature in 5% bovine serum albumin (BSA) for phosphorylated MAPK-p38 (P-p38) and in milk for NK1R. An overnight incubation at 4 °C was then performed with primary antibodies: anti-P-p38 (1:1000; Phospho-p38 MAPK (Thr180/Tyr 182)

(D3F9) XP[®]; Cell Signaling Technology[®], Leiden, The Netherlands) or anti-NK1R (1:1000; NB300-119; Novus biologicals, LLC, CO 80112, USA) from rabbit. All antibodies were diluted in a blocking solution. After three washes, a one-hour incubation was performed with a peroxidase-conjugated IgG secondary antibody from goat anti-rabbit (1:5000; Santa Cruz Biotechnology, Tebu-Bio, Le Perray en Yvelines, France). After three additional washes, immunocomplexes were revealed using the BIO-RAD Clarity™ Western ECL substrate (luminol/enhancer and peroxide solutions; Bio-Rad Laboratories, Inc. CA 94547, USA). Proteins were quantified by densitometry using BIO-RAD ChemiDoc™ XRS+ with Image Lab™ software (version 6.0.0 build 25 Standard Edition © 2017, Bio-Rad Laboratories, Inc. CA 94547, USA), and normalised for total protein.

Measurement of gastric and colonic paracellular permeabilities

After euthanasia, stomach and distal colon samples were removed on days 2 and 7 according to the group. Samples were cut along the mesenteric border. Gastric and colonic permeabilities were assessed by measuring Lucifer yellow CH dilithium salt (luciferase L0259; Sigma-Aldrich Co., MO 63103, USA) and dextran Alexa Fluor™ 680 (Fisher #11555336 Invitrogen™ by Thermo Fisher Scientific; Life Technologies Corporation, OR 97402, USA) fluxes in Ussing chambers with an exchange surface of 0.07 cm² (Harvard Apparatus, Holliston, MA, USA) as previously described (Beutheu et al., 2014). Lucifer yellow (250 µg/mL) and Alexa (2 µg/mL) in HBSS was loaded on the mucosal side. Lucifer yellow (457.25 Da) was used to assess fluxes of small molecules, while Alexa (3-10 kDa) was used to assess fluxes of big molecules. After three hours at 37 °C, the medium from the contralateral side (serosa) was removed and stored at -80 °C. The fluorescence levels of Lucifer yellow (excitation at 428 nm, emission at 540 nm) and Alexa (excitation at 665 nm, emission at 710 nm) were measured in a 96-well black plate using the Spark[®] microplate reader (Tecan Group Ltd., Männedorf, Switzerland), analysed using SparkControl Magellan™ software (version 3.0; Tecan Group Ltd., Männedorf, Switzerland), and were used for analysis.

Statistical analysis

The data were expressed as mean $\pm$ SEM. Quantitative data were compared between groups using a non-gaussian unpaired t-test (Mann-Whitney test). Comparisons of multiple groups were performed using one-way ANOVA (Kruskal-Wallis test) with post-hoc analysis (Dunn's multiple comparison post-test to compare all pairs of columns to each other). A p-value < 0.05 was considered statistically significant. Outliers were identified using the ROUT method (robust regression and outlier removal) with a maximum false discovery rate of 0.1% to remove only definitive outliers (Motulsky and Brown, 2006). All statistical analyses were performed using GraphPad Prism version 9.4.0 for Windows (GraphPad Software Inc., San Diego, CA, USA, www.graphpad.com).

11.6. Results

Baseline data of the first series

Rats had the same age and weight on the day of the experiment. The TNBS dose instilled in the colon was 75.1 ± 1.10 mg/kg. Rats lost weight on day 2 in the TNBS group compared to controls ($p < 0.0001$) but regained their lost weight for day 7. Stools were looser in the TNBS groups on day 1 in comparison to the control group ($p < 0.005$). Colonic weight was heavier on days 2 and 7 in TNBS groups compared to controls ($p < 0.05$), whereas colonic length was similar between groups ($p = 0.10$). Colonic weight-length ratio was therefore greater in TNBS groups on days 2 and 7 compared to controls ($p < 0.05$). Gastric weight remained unchanged between group ($p = 0.31$). The MaS assessing colitis in rats was increased only in TNBS groups ($p < 0.005$). The death rate was similar in all groups (20.0%, 18.2% and 21.0% in controls, TNBS D2 and TNBS D7 respectively, $p = 0.94$). The same amount of phenobarbital was used to sedate animals in all groups ($p = 0.13$). All results are shown in Supplementary table 7.1.

Inflammatory parameters and permeability assessment

No differences were found at day 2 and day 7 in MPO activities between animals in which TNBS or saline was administered in the colon (Figure 11.1).

Plasmatic concentrations of IL-1 β , IL-6 and IL-10 were also not different between the different groups at days 2 and 7 ($p = 0.075$, 0.054 , and 0.17 respectively), as shown in Figure 11.2. Plasmatic concentration of TNF- α was undetectable in the majority of samples.

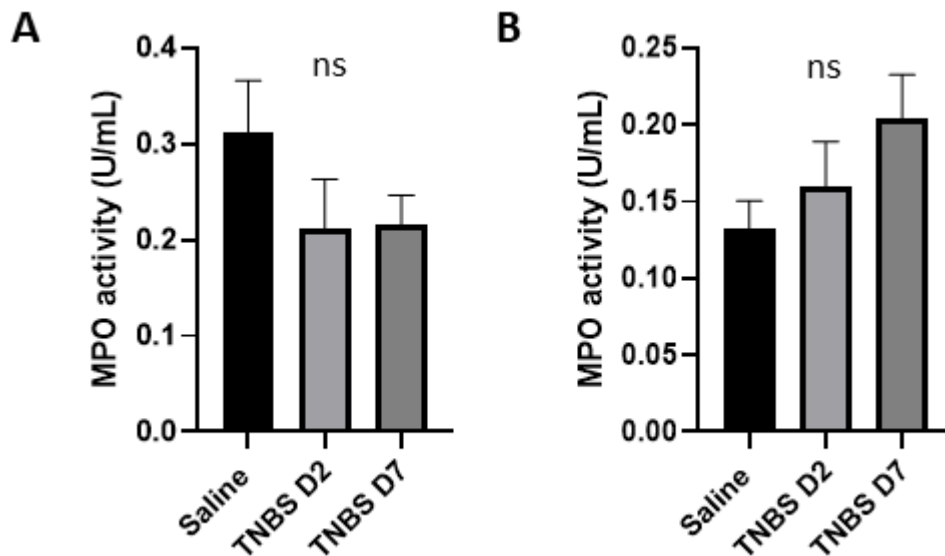


Figure 11.1. Gastric and colonic inflammation.

Gastric (A) and colonic (B) inflammatory levels assessed by myeloperoxidase (MPO) activities are not different between rats with intracolonic administration of saline (NaCl 0.9%) or TNBS (25mg) on day 2 (D2) and day 7 (D7). $N = 9-13$ rats per group. Variability in the results is represented by the standard error of the mean.

ns: non-significant, TNBS: 2,4,6-trinitrobenzene sulphonic acid, U: unit.

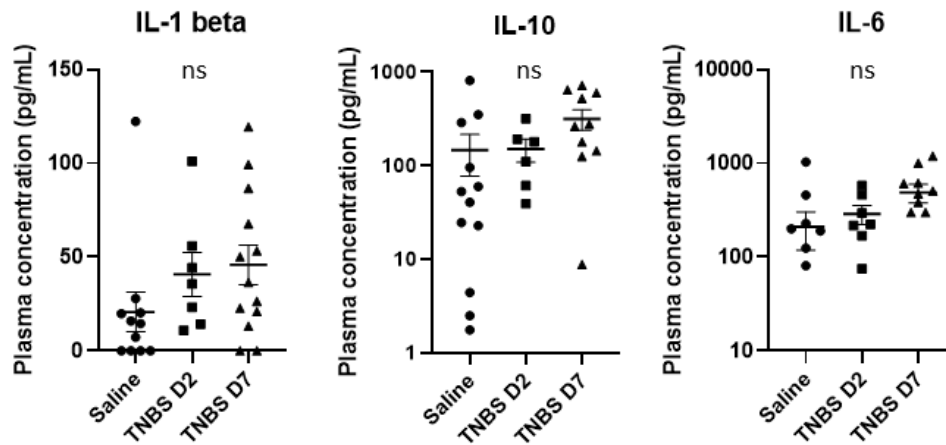


Figure 11.2. Observed concentrations of plasmatic inflammatory cytokines. Plasmatic concentrations of IL-1 β , IL-6 and IL-10 using multiplex assay are not different between rats with intracolonic administration of saline (NaCl 0.9%) on day 7 or TNBS (25mg) on day 2 (D2) and day 7 (D7). $N = 7-13$ rats per group. Variability in the results is represented by the mean and the standard error of the mean.

* $p < 0.05$ (comparison between TNBS D2 and TNBS D7 to the saline group)

IL: interleukin; ns: non-significant, TNBS: 2,4,6-trinitrobenzene sulphonic acid.

No differences were found at days 2 and 7 in gastric or colonic permeabilities (Figure 11.3).

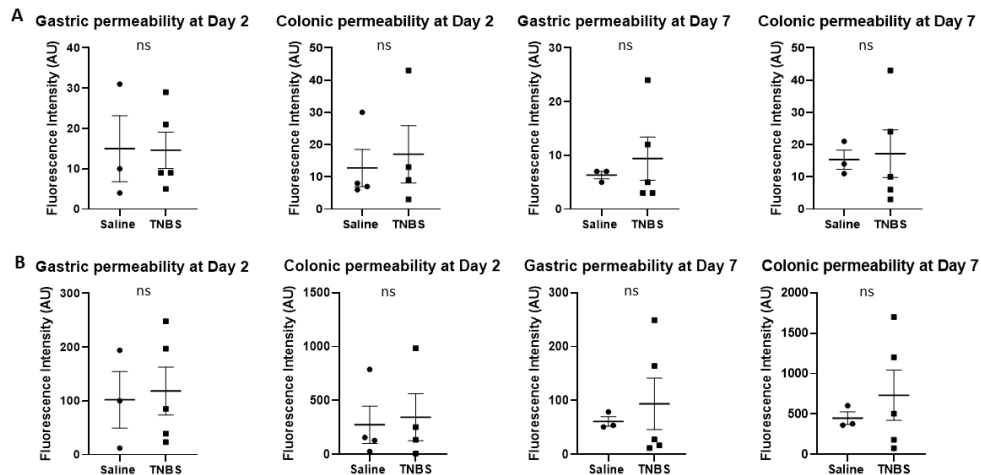


Figure 11.3. Gastric and colonic permeabilities.

Permeabilities assessed by Alexa (A) and Lucifer yellow (B) are not different between rats with intracolonic administration of saline (NaCl 0.9%) or TNBS (25mg) on days 2 and 7. $N = 3-5$ rats per group. Variability in the results is represented by the mean and the standard error of the mean.

AU: arbitrary unit, ns: non-significant, TNBS: 2,4,6-trinitrobenzene sulphonic acid.

Development of the rat model of colon-stomach cross-sensitisation

A single intra-colonic administration of 25mg of TNBS induced an increase of the colonic and gastric nociceptive responses during colorectal and gastric distensions respectively in rats on day 7 compared to those with administration of saline. Increased gastric nociceptive responses during gastric distensions were observed at 20 mmHg ($p = 0.0006$), 30 mmHg ($p = 0.025$) and 40 mmHg ($p = 0.0062$) but not at 60 mmHg ($p = 0.066$) on day 7 (Figure 11.4A). Increased colonic nociceptive responses during CRD were observed at 60 mmHg ($p = 0.044$) on day 7 (Figure 11.4C). Increased gastric nociceptive responses during gastric distensions were already observed at 40 mmHg ($p = 0.017$) on day 2 (Figure 11.4B) but no increased colonic nociceptive responses during CRD were observed on day 2 (Figure 11.4C). Further experiments were therefore designed to understand the mechanisms of the chronicization of cross-sensitisation in this model.

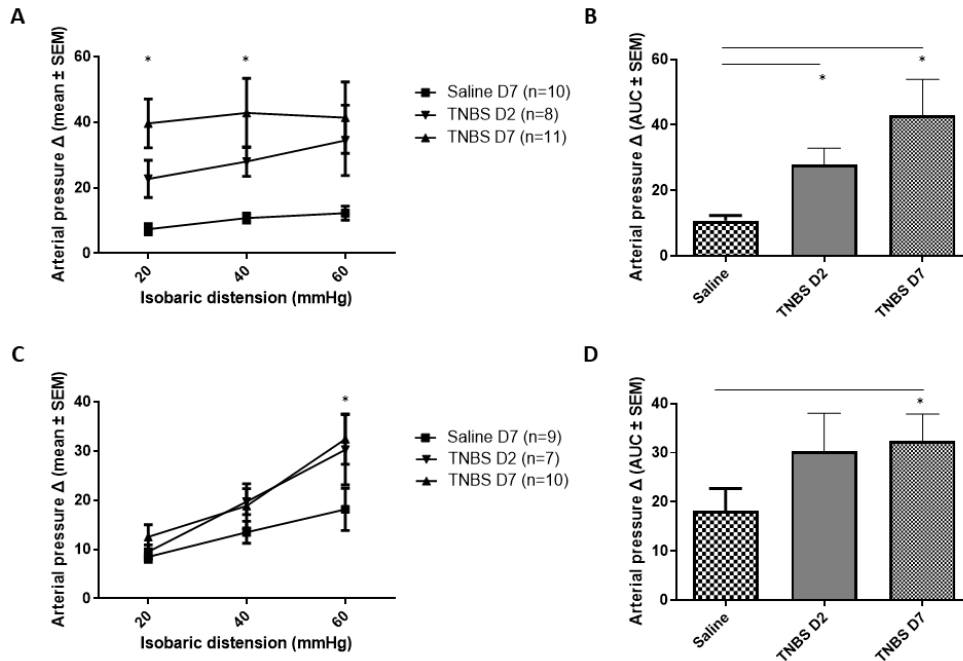


Figure 11.4. Visceromotor response to gastric and colorectal distensions.

Visceromotor response to gastric and colorectal distensions in rats with intracolonic administration of saline (NaCl 0.9%) on day 7 or TNBS (25mg) on day 2 (D2) and day 7 (D7). Variations in arterial pressure in response to isobaric distensions at 20-40-60 mmHg in the stomach (A) and the colon (C) is shown on the left, with details at 40 mmHg of gastric distension (B) and 60 mmHg of colorectal distension (D) on the right. $N = 7-11$ rats per group. Variability in the results is represented by the mean and the standard error of the mean.

* $p < 0.05$ (comparisons to the saline group)

Δ : variation, AUC: area under the curve; SEM: standard error of the mean, TNBS: 2,4,6-trinitrobenzene sulphonic acid.

Implication of central microglia in colon-stomach cross-sensitisation

We administered intrathecally minocycline, a microglial inhibitor, two minutes before the administration of TNBS in the colon to demonstrate the involvement of microglial cells. A group with intraperitoneal injections of LPS was added as inflammatory control. Increased gastric nociceptive responses during gastric distensions were observed at 20 mmHg ($p = 0.024$) on day 7 (Figure 11.5A).

Intrathecal injection of minocycline prevented the development of cross-sensitisation induced by TNBS administration in the colon ($p > 0.99$). Increased colonic nociceptive responses during CRD were observed at 60 mmHg ($p = 0.026$) on day 7 (Figure 11.5B). Intrathecal injection of minocycline prevented the development of visceral hypersensitivity induced by TNBS administration in the colon ($p = 0.13$). Intraperitoneal administration of LPS did not induce visceral hypersensitivity to the colon or the stomach. No mortality occurred in the LPS group.

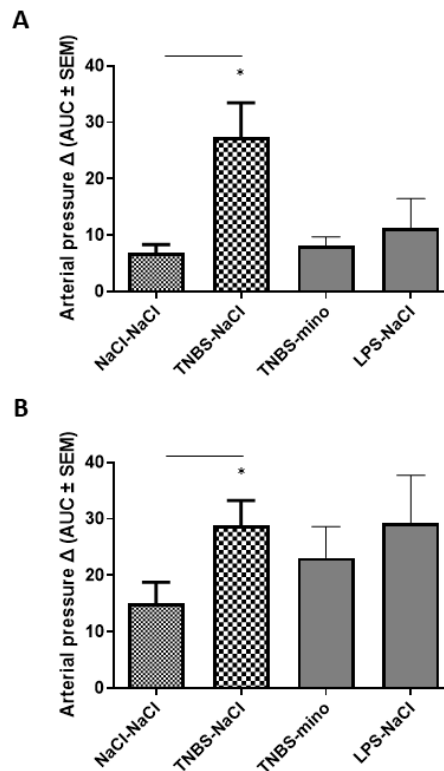


Figure 11.5. Effect of intrathecal injection of minocycline on visceral sensitivity. Variations in arterial pressure in response to isobaric distensions at 20 mmHg in the stomach (A) and 60 mmHg in the colon (B) in rats with intrathecal injections of saline (NaCl 0.9%) or minocycline ("mino", 1.25 mg/kg) prior to intracolonic administration of saline (NaCl 0.9%), TNBS (25mg) or intraperitoneal injection of LPS (from *Escherichia coli* 0111:B4, 1mg/kg) on day 7 are shown. $N = 8-18$ rats per group (13 in NaCl-NaCl group, 18 in TNBS-NaCl group, 8 in TNBS-mino group and

10 in LPS-NaCl group). Variability in the results is represented by the mean and the standard error of the mean.

* $p < 0.05$ (comparison between TNBS-NaCl and the saline-saline group)

Δ : variation, AUC: area under the curve; LPS: lipopolysaccharide, SEM: standard error of the mean, TNBS: 2,4,6-trinitrobenzene sulphonic acid.

Involvement of central phosphorylated MAPK-p38 in colon-stomach cross-sensitisation

A single intra-colonic administration of 25mg of TNBS induced a decrease of the expression of P-p38 assessed by WB at the T8-T9 level of the spinal cord on day 2 compared to the saline group ($p = 0.033$), with a return to baseline on day 7 ($p = 0.77$), as shown in Figure 11.6.

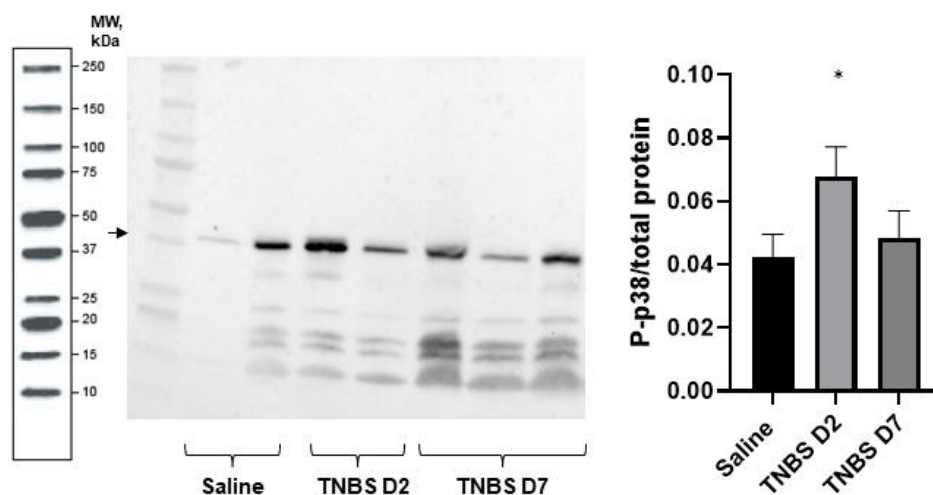


Figure 11.6. Expression of phosphorylated MAPK-p38.

Expression of phosphorylated MAPK-p38 (P-p38) at the T8-T9 level of the spinal cord, with quantitative analysis (ratio to total proteins) on the right, in rats with intracolonic administration of saline (NaCl 0.9%) at the day 7 or TNBS (25mg) on day 2 (D2) and day 7 (D7). Protein ladder for MW determination is shown on the left; the arrow corresponds to the MW of P-p38 (41 kDa). $N = 8-14$ rats per group.

Variability in the results is represented by the mean and the standard error of the mean.

* $p < 0.05$ (compared to the saline group)

MAPK: mitogen-activated protein kinases, MW: molecular weight, TNBS: 2,4,6-trinitrobenzene sulphonic acid.

Assessment of the expression of spinal pro- and anti-inflammatory cytokines

Levels of *TNF- α* , *IL-1 β* and *IL-10* mRNAs transcripts at the T8-T9 level of the spinal cord did not differ between groups on days 2 and 7 ($p = 0.48, 0.11$ and 0.57 respectively), as shown in Figure 11.7.

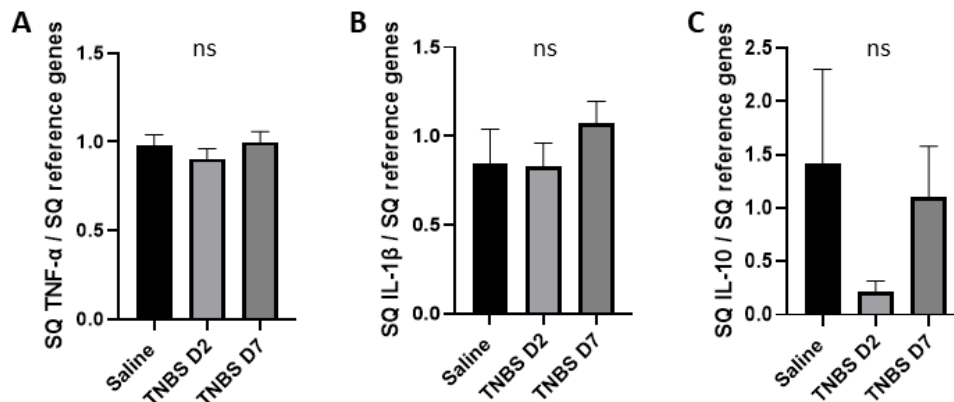


Figure 11.7. Expression of pro-inflammatory cytokines in the spinal cord.

Expressions of *TNF- α* (A), *IL-1 β* (B) and *IL-10* (C) mRNAs at the T8-T9 level of the spinal cord assessed by RT-qPCR are not different between rats with intracolonic administration of saline (NaCl 0.9%) or TNBS (25mg) on day 7. Results are expressed as the ratio between starting quantities (SQ) of the target cytokine to the reference genes. $N = 8-13$ rats per group. Variability in the results is represented by the mean and the standard error of the mean.

IL: interleukin, mRNA: messenger ribonucleic acid, ns: non-significant, RT-qPCR: reverse transcription quantitative polymerase chain reaction, SQ: starting quantity, TNBS: 2,4,6-trinitrobenzene sulphonic acid, TNF: tumour necrosis factor.

Participation of central NK1R in colon-stomach cross-sensitisation

A single intra-colonic administration of 25mg of TNBS induced a decrease of the expression of NK1R assessed by WB at the T8-T9 level of the spinal cord on day 7 compared to the saline group ($p = 0.049$), as shown in Supplementary figure 7.1.

11.7. Discussion

We describe a new chronic rat model of cross-sensitisation between the colon and the stomach following an acute inflammatory insult. Our study shows that cross-sensitisation between lower and upper GI tract involves central sensitisation and microglial interactions mediated by the MAPK-p38 pathway. Colonic inflammatory insult of rat pups was already shown to induce gastric hypersensitivity in adult life (Winston and Sarna, 2013) but our model is the first to describe this phenomenon in older animal and to evidence the implication of central sensitisation.

Our model fulfills criteria required for animal models of cross-organ sensitisation (Qiao and Tiwari, 2020). Indeed, our inflammatory insult was limited to a specific organ, the colorectum, since inflammatory cytokines was not elevated in the early phase after the inflammatory insult. Previous studies showed that TNBS-induced colitis mainly induces a Th1-Th17 response, with increased IL-12 and IL-17 levels (Alex et al., 2009). Furthermore, visceral hypersensitivity was found in another organ than the irritated one, as evidenced by the increased nociceptive response during gastric distensions in the TNBS groups. Finally, direct injury to the cross-sensitised organ was avoided since no macroscopic inflammation was evidenced at the gastric level during necropsy and gastric weight remained unchanged between groups. Several markers confirmed the impact of the acute inflammatory insult in the colorectum: rats in the TNBS groups lost weight, stools were looser in TNBS groups on day 1 despite a likely bias (excessively liquid stools could not be collected in TNBS groups), the macroscopic score assessing colitis in rats was increased in TNBS groups, colonic weight-length ratio was greater in TNBS groups as a consequence of mucosal thickening and tissue oedema (whereas it is a marker of fibrosis in chronic states) and the TNBS dose instilled in the colon was about 75 mg/kg, i.e. higher than the

optimum dose of 50 mg/kg for the highest reproducibility of colonic damage with the least mortality rate which has been published (Motavallian-Naeini et al., 2012).

Mechanisms of the chronicization of cross-sensitisation in our model involve neural pathways. Indeed, no systemic inflammatory reaction was evidenced and an inflammatory assault is therefore unlikely to explain cross-activation. Colonic distension inhibits the gastric adaptive relaxation, suggesting the existence of a colo-gastric relationship in rats (Uchida and Iwamoto, 2014). Previous work showed that non-inflammatory upregulation of NGF underlies gastric hypersensitivity induced by neonatal colonic inflammation in rats (Li et al., 2016). The IT injection of minocycline prevented the development of cross-sensitisation induced by TNBS administration in the colon in our model. Since minocycline is an inhibitor of the microglia, cross-activation seems to be mediated by spinal microglial activation. Intrathecal minocycline was shown to attenuate peripheral inflammation-induced hyperalgesia by inhibiting MAPK-p38 in spinal microglia (Hua et al., 2005). Furthermore, the changes in the expression of P-p38 in the spinal cord between TNBS and control groups is in favour of the involvement of this pathway in the development of colon-stomach cross-sensitisation. The expression of P-p38 in the spinal cord was increased at day 2 whereas the expression of NK1 receptor was decreased at day 7 after the colonic administration of TNBS compared to saline. Substance P is known to activate the MAPK-p38 pathway through NK1R (Chakraborty et al., 2011). Since an upregulation of P-p38, the activated form of MAPK-p38, is observed in our model on day 2, the downregulation of NK1R on day 7 is probably a compensatory phenomenon.

The mechanisms involved in microglial activation at the central level are unknown, however. Indeed, the levels of spinal pro- and anti-inflammatory cytokines were similar between groups. Interactions between neurons, microglial cells and immune cells have been shown to have a key role in cross-organ sensitisation (Qiao and Tiwari, 2020). Spinal trans-segmental pathways could be involved. Indeed, CGRP is involved in central spinal sensitisation (Kay et al., 2013). Calcitonin gene-related peptide generally activates a cyclic adenosine monophosphate (cAMP)-signalling pathway and is known to increase the activity of MAPK-p38 via CGRP type 1 receptor (Russell et al., 2014). CGRP also contributes to the development of tolerance to morphine-induced analgesia by

regulating the activation of microglial MAPK-p38 (Wang et al., 2010). Since CGRP is a classic molecular marker of peptidergic C fibers and that the sprouting of those nerve fibers occur in the spinal cord following TNBS-induced colitis in the rat (Qiao and Grider, 2009), this pathway could be investigated in the future.

Supra-spinal sensitisation could also be implicated since minocyclin also inhibits microglia in the brain. Microglial remodeling in the central nucleus of the amygdala was previously shown to contribute to chronic stress-induced visceral hypersensitivity *via* microglial MAPK-p38 activation, glucocorticoid receptor dysfunction, and synaptic plasticity (Yuan et al., 2020b). The inhibition of microglial activity in the amygdala was sufficient to reduce visceral hypersensitivity in this work (Yuan et al., 2020b).

We have chosen rats since gastric barostat require a sufficient size of the stomach to be performed, and Sprague-Dawley strain since the Wistar-Kyoto strain is known to be spontaneously more stress-sensitive (Pare and Tejani-Butt, 1996). Among the different models of visceral hypersensitivity which have been developed (Moloney et al., 2015), we have chosen chemical sensitisation not to have pan-intestinal effect *per se*. Since the models being used only induce segmental inflammation, it enables us to assess if cross-organ sensitisation occurs. Transmural inflammation induced by TNBS compared to mucosal inflammation by AA, with negative results (data not shown). We used the dose of minocycline of 1.25mg/kg in our work based on published results from other research teams (Mei et al., 2011, Deng et al., 2019). We would have expected a dose-dependent effect of minocycline like it has been reported by other groups at the peripheral level (Cho et al., 2012) and at the central level (Hua et al., 2005). However, we only tested the most appropriate dosage in order to reduce the number of animals involved in the study (reduction principle of the 3Rs). We measured visceral pain to gastric and colorectal distensions using changes in the arterial blood pressure as a surrogate marker of visceral sensitivity as previously described by our group (Meleine et al., 2020).

Our work includes some limitations. Our results were subject to high heterogeneity of response in the TNBS model. Various factors influencing the response to TNBS-induced colitis in *Rattus norvegicus* have been reported: the TNBS dosage, the TNBS/ethanol ratio, the strain of the rat, the age of animals, their weight, housing conditions of the animals and their gut microbiota (Antoniou et al., 2016). Gut microbiota taxa are a source of variability in a mouse model of

colitis (Forster et al., 2022, Benech and Sokol, 2022). Trinitrobenzene sulphonic acid-induced colitis was shown to induce mild, moderate and severe colitis in male Wistar rats (Ferreira-Duarte et al., 2021). About one-quarter of rats develop chronic visceral hypersensitivity 16 weeks following TNBS-induced transient colitis (Zhou et al., 2008). These two studies (Zhou et al., 2008, Forster et al., 2022) involved 20/28 controls and 75/87 treated rats, respectively; our study is therefore possibly underpowered due to the low number of rats included. Mechanistic aspects have been incompletely explored; especially, we did not assess changes in the number of microglial cells or their phenotype and we did not assess the effect of blocking P-p38. Increased colonic nociceptive responses during CRD were still present at the time we assessed gastric sensitivity; longer term experiments are needed to confirm that our cross-sensitisation is long-lasting. We used a hypnotic drug to sedate our animals but its influence on the results is unlikely since the same amount of phenobarbital was used in all groups; this could therefore not explain a lack of nociceptive response or other functional dysfunctions in some groups. Thiobutabarbital was shown to have little influence on digestive motility compared to isoflurane for instance (Ailiani et al., 2014). Finally, innervation of the gut differs between rats and humans, with limited innervation of the proximal colon by the vagus nerve in humans; relevance to human biology is therefore limited. Even if the vagus nerve innervates both the stomach and proximal colon in rats, it is unknown if some neurons co-innervate the stomach and the colon. In humans, visceral hypersensitivity to distension is organ-specific in patients exhibiting IBS or FD alone but pan-intestinal in patients with IBS+FD overlap (Bouin et al., 2004). However, supra-spinal crosstalk could happen in humans and explain cross-sensitisation between both organs.

11.8. Conclusion

In conclusion, we describe a new model of chronic cross-organ visceral sensitisation between the colon and the stomach in rats following an acute insult. TNBS-induced colitis induces long-lasting colorectal and gastric hypersensitivities to distension, mediated by upregulation of MAPK-p38 pathway. Future experiments should assess microglial activation and the effect of a MAPK-p38 blocker in our model.

11.9. Concluding paragraph

Summary of the main findings

- A new model of cross-organ visceral sensitisation between the colon and the stomach has been developed in rats.
- TNBS-induced colitis induces long-lasting (7 days) colonic and gastric hypersensitivities to distension.
- Colon-stomach cross-sensitisation is mediated by neuroglial activation and upregulation of MAPK-p38 pathway in this model.

Inferences

- A colon-stomach chronic cross-sensitisation rat model using intra-colonic TNBS administrations can be used as a preclinical model of overlap between FD and IBS.
- Microglial interactions are central in colon-stomach cross-sensitisation.

Perspectives

- Assess the activation of microglia by immunostaining for Iba1 or TMEM119.
- Assess the effect of a MAPK-p38 blocker (SB203580, etc.).
- Confirm the results on the longer-term.

Dissemination

- None. The data presented in this chapter have not been submitted yet at the time of the printing of the manuscript.

Impact of the research

- None.



Chapter 12 GENERAL DISCUSSION

12.1. Overview of the results

STUDYING OVERLAPS BETWEEN DIFFERENT DGBI and between DGBI and other non-GI disorders is important because (1) it has the potential to offer clues about the aetiology and pathophysiology of those disorders, (2) their management is more complex, (3) the impact on patients' lives is greater (symptom burden, mental health, QoL, etc.), (4) those patients have more medication prescriptions, (5) health costs are increased in this population (Lee and Chang, 2021), among other things. Our work has increased our knowledge in this field; an overview of our results is given in this chapter.

Neurogastroenterology is the field of study of GI motility disorders and DGBI. Disorders of gut-brain interactions are defined by symptom-based consensus definitions, similar to functional somatic disorders such as fibromyalgia, CFS, chronic pelvic pain, migraine, and so on. Symptom clusters define each DGBI (Clevers et al., 2018). However, the inclusion of some symptoms in a specific DGBI has sometimes changed over time. For example, heartburn was previously part of FD (reflux-like subtype), but FD and GORD are now distinct entities. Nausea and vomiting are also exemplary of those symptom clusters, with their belonging to the dyspeptic spectrum being challenged at each iteration of the Rome criteria. We compared patients with CNVS, FD and their overlap, and showed that patients with overlapping FD+CNVS behave like FD patients with a more severe disorder (Chapter 6 Article 3).

Clinical history is essential in arriving at a diagnosis of DGBI, as William Osler (1849-1919) said over a century ago: "Listen to the patient; he is telling you the diagnosis" (Aronson, 2022). However, it is challenging to rely on symptoms for diagnosis since cultural, linguistic, religious, and socio-economic factors are known to alter their understanding by patients (Mahadeva and Ford, 2016, Chuah and Mahadeva, 2018). Some patients confuse postprandial fullness with a sensation of bloating (Carbone et al., 2014), and there is no translation for bloating in Spanish (Rabago et al., 2022). Similarly, the meaning of the term discomfort varies greatly among IBS patients. This partially led to a change in the Rome definition of the disorder, with only patients reporting pain having IBS

according to Rome IV criteria (Lacy et al., 2016). It is also challenging to discriminate retching (*hauts-le-cœur* in French) as a dyspeptic symptom from nausea (*nausées* in French), and to identify regurgitation based on a self-questionnaire. Some common symptoms described by patients who suffer from upper GI disorders also have no precise counterpart in medical terminology (Heading et al., 2016). Even physicians and experts in the fields disagree on the terminology. For instance, satiation (*rassasiement* in French) and satiety (*satiété* in French) are often used indistinguishably, although the terms refer to different physiological states: satiation is the feeling of fullness during a meal, whereas satiety is the feeling of fullness between meals (Klaassen and Keszthelyi, 2021). The characteristic symptom of the PDS subtype is, therefore, *early satiation* and not *early satiety* (even if it is always erroneously translated in French by *satiété précoce*) (Stanghellini et al., 2016).

Nosology is the division of medicine dealing with the classification of diseases, similar to the nomenclature used for plants by Carl von Linné in its *Systema Naturæ* in 1735 (Linnæus, 1735). Classifying a medical condition is influenced by the knowledge about its pathophysiology, as it has been done with taxonomy for living species since Darwin in its *Origin of Species* in 1859 (Darwin, 1859). We propose classifying them arbitrarily into four groups: overlaps with somatic diseases, with another DGBI, with non-GI functional disorders, and with psychological factors/psychiatric conditions. Building a classification for comorbidities and overlap syndromes associated with FD was difficult, especially because some disorders belong to different groups (e.g. restless leg syndrome is a disorder with central hypersensitivity but is also a sleep disorder) and some are suspected to be pathomechanisms rather than separate comorbidities (e.g. SIBO). This classification will probably be a subject of debate. For example, the Overlap in DGBI Working Team of the Rome Foundation classifies overlaps with a DGBI into three groups: overlaps among different DGBI, with non-GI symptoms/syndromes and with organic diseases.

Symptoms of distinct DGBI are often present in a single patient. Indeed, overlaps between different DGBI are commonly found in community-based studies, especially between FD, IBS and GORD. Overlap between GORD and Rome III-based FD was present in 4.1% of the US population, compared to the 1.1% which would have been expected by chance (Choung et al., 2012). For instance, an overlap between IBS and FD was also present in 10.0% of a random sample of the

Swedish population (Agréus et al., 1995). Approximately one-third of patients have a DGBI in at least two anatomic regions (Aziz et al., 2018b). Overlap syndromes and association with comorbidities are, therefore, the rule rather than the exception in DGBI. Our systematic review demonstrated that comorbidities and overlap syndromes are common in FD (Chapter 3 Article 1).

Our systematic review identified gaps in knowledge about the presence of comorbidities in FD patients (Chapter 3 Article 1). We have filled a void by describing for the first time the prevalence of BPS in FD patients (Chapter 8 Article 5). No data on the prevalence of fibromyalgia among FD patients was reported in the medical literature (Erdrich et al., 2020). We found a prevalence of 6.8% in our tertiary-care population (Chapter 5 Article 3), compared to a pooled prevalence of 1.6% in the French population (Perrot et al., 2011), which would make an OR of 4.49. However, this result should be taken with caution and only reflects our tertiary-care population since a selection bias is likely. Patients with FD suffering from rumination syndrome have fibromyalgia in 7.1% of the cases (Josefsson et al., 2022a), in concordance with our results. We found a prevalence of 35.8% of self-reported migraine in the same cohort, which is similar to the reported prevalence of 42.8% in a population-based study in the USA (Zand Irani et al., 2021). We also found chronic fatigue to be reported by 39.2% of FD patients in our cohort.

The frequent association of different comorbidities and diseases with FD could be due to chance alone, especially since DGBI are very common in the community. Describing the prevalence of a comorbid condition in FD is therefore insufficient to prove that common pathomechanisms mediate the association. Demonstrating that there is an interplay between conditions requires either showing that the prevalence in FD is higher than in a control group or that it is significantly higher than expected by chance. As we did not have a control group from the general population in our work about the overlap with IBS and BPS in FD (Chapter 8 Article 5), we could only apply the second methodology. The overall population was composed of 1,453 patients, of whom 61.4% had FD (892/1,453), 31.2% IBS (454/1,453) and 22.7% BPS (330/1,453). Co-occurrence of FD and IBS was observed in 20.2% (294/1,453) compared to the 19.2%, which would have been expected by chance ($0.614 \times 0.312 = 0.192$, $p = 0.48$). Overlapping FD-BPS was found in 16.5% (240/1,453) compared to 13.9%, which would have been expected by chance ($0.614 \times 0.227 = 0.139$, $p = 0.0497$). Similarly, FD+IBS+BPS

overlap was observed in 7.4% (107/1,453) compared to the 4.3%, which would have been expected by chance ($0.614 \times 0.312 \times 0.227 = 0.043$, $p = 0.0004$)^d. The observed co-occurrences of FD+BPS and FD+IBS+BPS are, therefore, greater than would be expected by chance in our cohort sample.

Overlap between IBS, FD and heartburn (as a proxy for GORD) behaves as a distinct clinical entity characterised by more psychological distress, poorer sleep quality, more frequent association with asthma and greater stability over time compared to other DGBI (Jones et al., 2022). Similar conclusions could be drawn from our results on the association between FD, IBS and BPS (Chapter 8 Article 5), especially for the distinct cohort of patients overlapping FD+IBS+BPS. This could pave the way for identifying multiple patient subgroups if this observation is confirmed in other cohorts. Identifying distinct categories of patients would make it possible to test new therapeutic strategies in these populations.

Patients with overlap between multiple DGBI consistently suffer from greater symptom burden, worse psychological distress, and lower QoL (Choung et al., 2012, Lei et al., 2019a). These patients also have more work-related disabilities (Berens et al., 2020). Similarly, the overlap with non-GI functional somatic syndromes is associated with increased symptom severity in IBS assessed in primary care (Wang et al., 2023). Our results indicate the same thing for overlaps in FD. We studied the overlap with BPS and IBS in FD, and confirmed that these overlaps were associated with increased disease severity and poorer QoL in FD (Chapter 8 Article 5). A limitation of our work is that somatisation was not assessed, except indirectly, by mediation analysis. A validated score to assess somatisation should ideally be included in studies of comorbidities and overlaps in DGBI.

Delayed GE is present in 33 to 43% of patients with FD (Stanghellini et al., 1996, Wuestenberghs et al., 2019). However, the GE rate was unaffected by sleep quality or the presence of overlapping IBS, CNVS, BPS and migraine in our work. The link between GE and dyspeptic symptoms has also been the subject of many studies but remained debated. More generally, the effect of different

^d This data was analysed using GraphPad Prism 9 version 9.4.1 (681) for Windows® 64-bit (GraphPad Software Inc., San Diego, CA, USA, www.graphpad.com). We used a two-sample z-test for proportions (Chi-square test) to determine whether the two samples were drawn from the same population; a two-tailed p-value < 0.05 was considered statistically significant.

pathophysiological mechanisms (gastric hypersensitivity, impaired fundic accommodation and delayed GE) on symptoms reported by patients has already been investigated. Altered fundic accommodation is associated with early satiation in FD (Tack et al., 1998), and gastric hypersensitivity is associated with postprandial epigastric pain (Tack et al., 2001). We confirmed our hypothesis that GE was not a significant determinant of symptoms in dyspeptic patients, but it would be a major determinant in patients with the more severely delayed emptying (Chapter 7 Article 4). Since our publication, a meta-analysis found an association between optimally measured delayed GE and some upper GI symptoms (nausea, vomiting, abdominal pain and early satiation) (Vijayvargiya et al., 2019). The association between GE and dyspeptic symptoms has been evaluated from three other angles: by looking at the distribution of the meal in the stomach, by assessing symptoms during the test rather than over the period preceding the test, and by evaluating the importance of GE in relation to other pathophysiological mechanisms. Distinguishing intragastric meal distribution as proximal or distal was shown to be associated with patient symptoms (Piessevaux et al., 2003, Silver et al., 2022). Patients with delayed GE and increased early distal meal distribution had more severe early satiation and regurgitation. In contrast, patients with delayed GE and increased late proximal meal distribution had more severe nausea, retching and vomiting (Silver et al., 2022). No correlations were observed between GE rate and the severity of symptoms (postprandial fullness, epigastric pain and burning, bloating, nausea and belching), assessed simultaneously during the test meal in patients with FD and idiopathic gastroparesis (Carbone et al., 2022a). Conversely, symptoms occurring during the test meal were correlated with daily symptoms in patients with diabetes mellitus (Kuwelker et al., 2021). Impaired accommodation, and perhaps visceral hypersensitivity, rather than GE, seem more important in explaining postprandial symptoms in patients with symptoms of gastroparesis (Karamanolis et al., 2007, Parkman et al., 2022b). Patients with gastroparesis-like symptoms have more frequently delayed GE than FD patients (Huang et al., 2023). In this work, delayed GE was associated with higher symptom severity in patients with gastroparesis-like symptoms (patients with diabetes were excluded) (Huang et al., 2023). Finally, improving GE does not necessarily improve symptoms in patients with delayed emptying (Wuestenberghs and Gourcerol, 2021a). In patients with gastroparesis,

the symptom improvement following prokinetic therapy is, in part, mediated by acceleration of GE, however (Goelen et al., 2023).

Our results about bladder-colon interactions in mice suggest that cross-organ sensitisation could explain the occurrence of colonic hypersensitivity following urinary tract infections in humans (Chapter 10 Article 6). Based on our results, a mechanistic model of cross-organ sensitisation can be proposed (Figure 12.1).

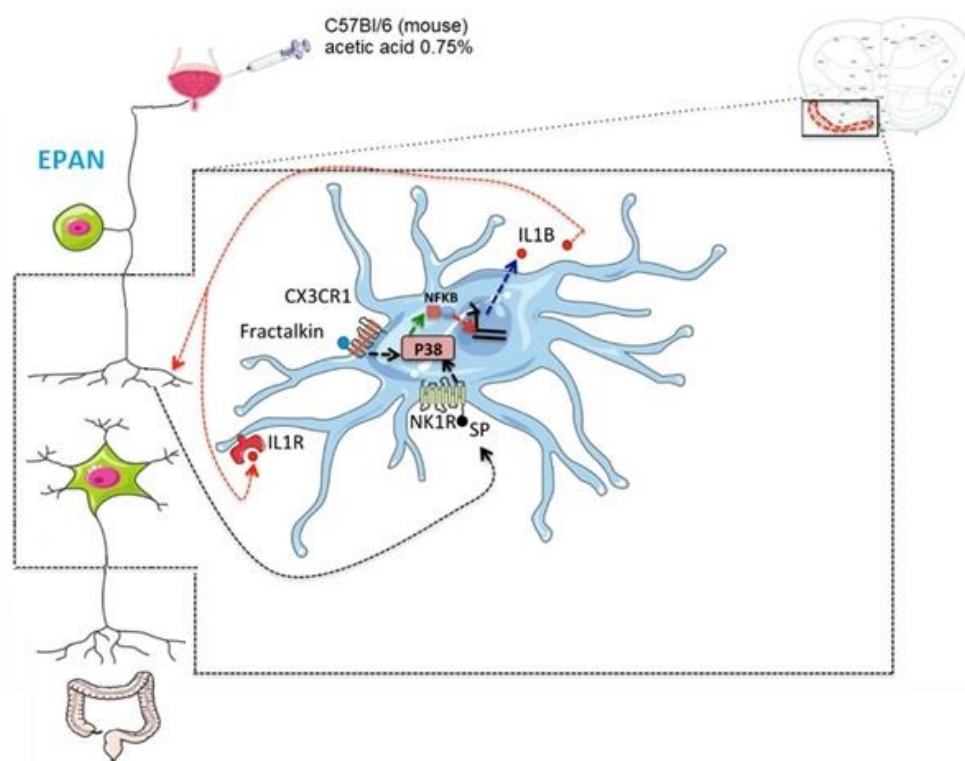


Figure 12.1. Diagram of molecular and cellular mechanisms underlying the development of visceral hypersensitivity by cross-sensitisation from the bladder to the colon.

Irritation of the urothelium by intravesical injections of acetic acid (0.75%) induces activation of extrinsic primary afferent neurons (EPAN), co-innervating the bladder and colon. These activated EPAN relaying to secondary afferent neurons (SAN) in the dorsal horn of the spinal cord secrete substance P (SP), a member of the tachykinin family. SP binds to Neurokinin-1 receptor (NK1R), which activates the Mitogen-Activated Protein Kinase (MAPK)-p38 by phosphorylation (P-p38), which

in turn could induce either directly or indirectly the synthesis of pro-inflammatory cytokines, such as interleukin-1 beta (IL-1 β) through the activation of the nuclear factor- κ B (NF κ B).

Adapted from Karim Atmani's thesis work (Atmani, 2018) with permission of the author.

Similarly, we developed a rodent model of cross-organ visceral sensitisation between the colon and the stomach (Chapter 11 Article 7). Our model adds to the understanding of cross-sensitisation between organs from different levels of the body. The caveats are the significant variability of our results in rodents, and that the interest of our model must be weighed against the difficulties of its implementation in the laboratory. The transposition of our results to humans is speculative given the difference in innervation between humans and rats and the fact that our results suggest cross-sensitisation occurs by neuronal pathway. Spinal trans-segmental cross-sensitisation could theoretically occur in human beings, however. A mechanistic model of cross-sensitisation between the lower and the upper GI tracts can be proposed based on our results: (1) following TNBS-induced colitis, sensory information is transmitted to the dorsal horn of the spinal cord, where (2) released mediators induce morphological changes, proliferation and differentiation/hypertrophy of the microglia and astrocytes; (3) activation of non-neuronal cells (macrophages, SGCs, microglia and astrocytes) causes neuroinflammation in the spinal cord; (4) the formation of gap junctions between astrocytes also allows the transmission of information to remote areas of the spinal cord; (5) secretion of mediators at this level leads to retrograde sensitisation of central terminals of primary afferent neurons of the stomach, even if this organ is innervated by another segment of the spinal cord. Other mechanisms implicated in the overlap between FD and IBS should be investigated, and other models that do not involve cross-sensitisation should be developed for experimental studies. However, the role of microglia was emphasised in both animal models, which suggests targeting it in treatment trials in case of similar overlaps. Minocycline could theoretically diminish the development of colonic hypersensitivity in cases of cystitis or prostatitis, but the NNT would probably be high, and for an uncertain clinical significance.

Studying the association with sleep alterations in FD allowed us to assess the effect of a comorbidity on this disorder, and to study the causal links between

comorbidities and FD (Chapter 5 Article 2). Whether altered sleep is responsible for the development of FD, or is a consequence of the disorder, is still debated (Maneerattanaporn and Chey, 2009). Independent factors predicting altered sleep quality in FD patients in our cohort were age (but not the duration of FD symptoms), depression levels and symptom severity. A vicious circle with dyspeptic complaints altering sleep induction or continuation and sleep deprivation exacerbating digestive complaints could explain the association we found between altered sleep quality and higher symptom severity. Of course, our work was not designed to prove causal relationships, which would require a prospective study. More generally, this raises the question of the direction of gut-brain interactions in DGBI (gut-to-brain or brain-to-gut?). For example, duodenal eosinophilia, a hallmark of FD, was shown to drive new-onset anxiety in the general population (Ronkainen et al., 2021). Still, anxiety increases the risk of developing FD (Aro et al., 2015), and duodenal eosinophilia is increased in FD (Shah et al., 2022), suggesting a complex interplay between all those factors, and another likely vicious circle. Presumably, the truth is mixed, with some patients having primary brain alterations while others have primary gut alterations. Indeed, independent gut-to-brain and brain-to-gut pathways have been shown in FD and IBS in a prospective study, with a primary mood disorder in two-thirds of the cases and primary gut disorder in one-third (Koloski et al., 2016).

Living with a DGBI alters QoL. Improving the QoL of patients suffering from DGBI is one of the main treatment goals in those disorders. It is, therefore, important to understand the determinants of QoL in these patients. In IBS, higher stool frequency, GI and overall somatic symptom severity, psychological distress and GI-specific anxiety were independently associated with reduced disease-specific QoL, the latter being the most critical factor (Melchior et al., 2022a). Rectal hypersensitivity and oro-anal transit time were not determinants of disease-specific QoL in this study. Mediating factors which could explain the effect of IBS on QoL are depressive symptoms for mental QoL, somatic symptom severity for physical QoL, and GI-specific anxiety for both dimensions of QoL (Trindade et al., 2022). Women had worse QoL compared to men in this study. Factors associated with decreased QoL in FD are anxiety and depression (Haag et al., 2008), increasing age (Hantoro et al., 2018), female gender (Talley et al., 2006a), greater symptom severity (Haag et al., 2008), low-to-mid educational level (Hantoro et al., 2018), somatisation (Van Oudenhove et al., 2011b), sleep (Chapter

5 Article 2), and overlap with other DGBI (Sperber et al., 2022). Gastric emptying is not a determinant of QoL in FD (Talley et al., 2006a, Haag et al., 2010), except probably for patients whose GE is most severely delayed (Chapter 7 Article 4). We have consistently shown in our works that overlap syndromes in FD have a detrimental effect on the QoL of those patients. The negative impact of overlapping DGBI on QoL has been confirmed by the Rome Foundation Global Epidemiology Survey recently: the more DGBI overlapping, the more altered the QoL (Knowles et al., 2022).

The subgroup of patients with overlapping DGBI could require another treatment. Indeed, those patients are known to be more difficult to treat (Madva et al., 2023). Treatment approaches in patients with overlapping DGBI include: focussing on the most bothersome symptom, prescribing a different treatment for each symptom or cluster of symptoms, or prescribing treatments with proven efficacy for the different DGBI. Asia-Pacific guidelines recently gave recommendations for treating these patients, but high-quality evidence needed to be provided for most of them (Gwee et al., 2023). In their work, they focussed on four clusters of patients based on factor analysis studies in Asia: FD overlapping with GORD, diarrhoea-predominant IBS (*EPS-IBS*), bloating (*PDS-IBS*) and constipation (Kwan et al., 2003, Siah et al., 2018). A multidisciplinary team approach could also improve patient care (Berens et al., 2020). Indeed, an unblinded randomised trial involving 188 IBS patients showed that multidisciplinary care improved clinical outcomes (symptoms), QoL, psychological state, and cost-effectiveness compared with standard care (Basnayake et al., 2020). This benefit was sustained 12 months after the completion of treatment (Basnayake et al., 2022). A matched cohort study involving IBS and FD patients also demonstrated superior short-term outcomes in a structured multidisciplinary care setting compared to standard care (Bray et al., 2022). This pleads for creating of care pathways for the most severe patients and more integrated care.

Behavioural and psychological factors both affect and are affected by DGBI, which is studied in the behavioural gastroenterology (Jia et al., 2017) and psychogastroenterology (Keefer et al., 2018) fields. Psychotropic drugs (mainly tricyclics) have a beneficial effect on FD patients (Ford et al., 2017, Ford et al., 2021). Patients suffering from FD have negative perceptions about medications, particularly in the presence of anxiety/depression comorbidities, and have a low willingness to initiate a central neuromodulator (Cassell et al., 2015). Promoting

behavioural changes, and targeting emotional or cognitive processes (GI-specific anxiety, hypervigilance to symptoms, and catastrophising), have been used in the treatment of FD, for example diet changes (Duboc et al., 2020) and internet-delivered cognitive behavioural therapy (Bonnert et al., 2019). Referral to gut-brain cognitive behavioural therapies may optimise patient care in some patients with DBGI (Keefer et al., 2022). Indeed, psychological treatment is beneficial in FD patients, but the level of evidence is low (Rodrigues et al., 2021). Patients failing first-line treatments are offered neuromodulators (Drossman et al., 2018). By contrast, there is a lack of evidence on whom to refer for behavioural therapies. Indeed, gut-directed behavioural therapies are far less studied in FD than IBS, in which recommendations have been published (Chey et al., 2021). Those therapies include GI-directed cognitive behavioural therapy, gut-directed hypnotherapy, mindfulness-based stress reduction and psychotherapy. Based on the knowledge in IBS patients, we can assume that patients who should be referred to the GI health psychologist are those who know that altered gut-brain interactions occur in FD, can identify the impact their symptoms have on their QoL, believe they have some control over their symptoms, have GI-specific anxiety or catastrophisation, have other somatic symptoms, accept to commit time to treatment, and in which stress exacerbates their symptoms (Chey et al., 2021).

Functional dyspepsia is a multifactorial syndrome to which the biopsychosocial disease model can be applied (Van Oudenhove et al., 2016b). This model emphasises the roles of psychological and social factors in diseases, beyond biological factors (Engel, 1977, Luo and Keefer, 2021). However, the case formulation based on this model has not been widely adopted by clinicians since the therapeutic value is limited. This model is even more suitable for patients with comorbidities, which could play as interfering factors. Similarly, the *Rome Foundation* developed a *multidimensional clinical profile*, focussing on managing difficult cases of IBS (Drossman, 2017). An alternative schema, the *3P* disease model, has, therefore, been developed to organise the factors that may contribute to the development of a clinical problem: predisposing factors (those putting at risk an individual), precipitating factors (those triggering the onset of the current situation), and perpetuating factors (those that maintain the problem after its beginning) (Spielman et al., 1987, Wright et al., 2019). More recently, a *4P* model has even been proposed, adding protective factors (those reducing the severity of the problem) to the list (Bolton, 2014); this disease model could be

applied to FD. Known predisposing factors include genetics (Garcia-Etxebarria et al., 2022), hormonal status (Sperber et al., 2021), neuroticism (Sharbafchi et al., 2020), alexithymia (Jones et al., 2004), anxiety (Aro et al., 2015), lower educational level (Kim et al., 2018a), altered sleep and somatisation (Gathaiya et al., 2009), and a history of childhood abuse (Oshima et al., 2015). Precipitating factors are different stressors, such as infection (Futagami et al., 2015) and surgery, psychosocial stress (De la Roca-Chiapas et al., 2010) and life events (Bennett et al., 1991). Perpetuating factors are the presence of other illnesses (IBS, etc.), lack of coping strategies (De la Roca-Chiapas et al., 2010), greater negative perception of adverse life events (Hui et al., 1991), compensatory behaviour (e.g. change in diet) (Carvalho et al., 2010), anxiety, depression, somatisation (Wilhelmsen et al., 1995, Aziz et al., 2018a), and adulthood abuse (Koloski et al., 2005b). Proven protective factors are scarce, with a low level of proof for adherence to a Mediterranean diet (Zito et al., 2016), for instance. Factors classified according to the biopsychosocial model of the disease are summarised in Table 12.1.

Table 12.1. Summary of potential predisposing, precipitating, perpetuating and protective factors across biopsychosocial domains in functional dyspepsia.

	Predisposing	Precipitating	Perpetuating	Protective
Biological	Genetics Gender	Acute infection Surgical or medical procedures	Chronic physical illness Overlap syndromes?	
Psychological	Personality traits Alexithymia Anxiety Altered sleep Somatisation	Stress	Lack of coping strategies Negative thoughts Compensatory behaviours? Anxiety Depression Somatisation	Coping skills Positive thoughts

Socio-environmental	Childhood abuse Poor socio-economic status Low educational level Geographic region	Life events	Adulthood abuse Smoking Lack of social support? Secondary gain?	Mediterranean diet Social support?

12.2. Directions for future research

Our results pave the way for further research and have some practical applications.

Clinical research

The systematic review of the medical literature identified gaps in knowledge, and found comorbidities and overlap syndromes for which no data was available. A population-based epidemiological survey could identify predefined comorbidities, with conditions diagnosed by a physician if necessary. The presence of a control group with healthy subjects would make it possible to identify the comorbidities associated with FD more frequently than chance would have allowed. Epidemiological studies could also investigate demographic and geographic differences associated with comorbidities in FD. The possibility of an overlap between FD and an organic disease in "remission" (such as uncomplicated diabetes, autoimmune gastritis or coeliac disease on a well-managed gluten-free diet) could also be evaluated.

Further work could involve studying possible risk factors of overlaps to understand their pathophysiology. Indeed, the pathomechanisms underlying overlaps between FD and another DBGI or a non-GI functional somatic disorder are poorly understood. Since somatisation implies experiencing multiple somatic symptoms without an underlying organic disease, greater somatisation scores could explain some overlaps. A prospective cohort study could identify factors associated with the development of comorbidities in FD patients, especially in PI-

FD. Given the significant attention to the future of patients with COVID-19 during the pandemic and the follow-up of patients with *long COVID*, i.e. patients with long-lasting symptoms following the resolution of SARS-Cov-2 infection (Davis et al., 2023), we can hope a better understanding of the pathomechanisms underlying functional somatic disorders in the following years. Since we found frequent overlap with allergic conditions, functional somatic disorders and psychological traits, special attention should be taken to study the role of immune dysregulation, central sensitisation and psychological features in the development of FD and overlapping conditions.

As our animal model suggests cross-sensitisation between the stomach and the colon, particularly to the stomach following an inflammatory colitis, a longitudinal study of patients with a first flare of inflammatory colitis, infectious colitis or acute diverticulitis could assess secondary onset of FD compared to a control group. Since cross-sensitisation between the bladder and the colon involves microglial interactions, minocycline could be assessed as a protective factor of colonic hypersensitivity following urinary tract infection or prostatitis, for example.

More specific patient cohorts could be identified among huge cohorts, as has been done with FD+IBS+heartburn and FD+IBS+BPS. Different subtypes have been identified in FD: EPS, PDS and EPS+PDS overlap. More recently, a latent class analysis identified four distinct subgroups characterised by varying degrees of GI symptoms, extra-intestinal symptoms and psychological factors (Barberio et al., 2021). Seven clusters were identified in IBS using the same method when symptoms (diarrhoea or constipation) were combined with psychological and neurological comorbidities, diet and lifestyle (Byale et al., 2022). Similarly, new subgroups of FD patients could be identified by taking into account the comorbidities of the disorder. Particular treatments could be assessed in those specific patient cohorts; cluster-oriented treatments could improve the management of those patients, especially those with comorbidities.

We only assessed subjective sleep in our work, but further studies could look at objective sleep with polysomnography in FD patients. Sleep could also be a therapeutic target in future clinical trials in this disorder. Indeed, a non-randomised trial involving 20 patients suggested that adding sleep aids could improve GI symptoms and QoL in FD patients (Nakamura et al., 2021).

The assessment of the overlap with symptom-defined BPS in FD was limited by the absence of urological assessment in our patients; we could guess that a new study, including urinalysis and cystoscopy in those patients, should yield a lower prevalence of BPS in FD. The interplay between FD, BPS and OAB could also be investigated.

A meta-analysis of studies evaluating the link between GE and digestive complaints of FD patients could be performed, with the difficulty of synthesising studies with multiple methodologies. Our results could also be replicated in a cohort assessed using gastric scintigraphy. Other physiological parameters could be similarly evaluated, particularly the link between pyloric distensibility (Wuestenberghs and Gourcerol, 2021b) and upper GI symptoms in FD. However, a recent meta-analysis found inconsistent correlations between electrogastrography (EGG) metrics and the presence and timing of FD symptoms (Varghese et al., 2021).

The effect of comorbidities on socio-economic factors such as absenteeism, healthcare costs, and health-seeking behaviour has been incompletely studied in FD, as is the possible protective factor of social support. Indeed, unemployment and divorce are risk factors for the disorder, and the mediation of those factors in its development should be assessed. The therapeutic value of case formulation using the *3P* or *4P* disease models could be assessed.

The management of patients with comorbidities and overlap syndromes is not codified and constitutes a challenge for clinicians, whom should avoid complex treatment combinations in these patients and rather target the predominant complaint. Clinical trials should evaluate the strategy of targeting the patient's main complaint or prescribing a combination treatment initially. It would also be interesting to determine whether patients with psychological comorbidities would benefit more from cognitive-behavioral therapies than those without.

Given the importance of psychological comorbidities in patients with overlap syndromes, the effect of neuromodulators and behavioural therapies could be evaluated in this population. The hypothesis could be that these treatments would show a greater benefit in patients with overlap than in patients with FD alone. In particular, a large, well-designed, sham-controlled trial of cognitive behavioural therapy is needed in FD patients with or without overlaps. Based on the model of chronic pain care, a collaborative approach involving

gastroenterologists, dieticians, hypnotherapists, psychiatrists, clinical psychologists, physiotherapists, and so on could also be investigated in patients with multiple overlaps/comorbidities.

The assessment of overlaps, comorbidities and disease modifiers is recommended in clinical trials concerning FD (Irvine et al., 2016). However, this recommendation is rarely followed until now (Wuestenberghs and Eugenicos, 2021). The influence of comorbidities and overlap syndrome on the results of RCTs needs to be assessed. It could improve the level of evidence in clinical trials in the field.

Experimental research

Perspectives for cross-organ sensitisation models between the upper and lower GI tracts could include the confirmation of our results in the longer term, assessing neuronal activation by c-fos and microglial activation (Iba1, TMEM119, etc.), mechanisms upregulating MAPK-p38 pathway (CGRP, etc.), testing other microglial inhibitors and, especially, a MAPK-p38 blocker (SB203580, etc.), assessing central levels of substance P, the effect of vagotomy, and evaluating the role of the sex of animals with female series.

We could test other cross-organ interactions, especially the stomach-duodenum and bladder-stomach. However, it would be challenging to assess stomach-duodenum crosstalks in small animals due to the proximity of both organs, even if convergence has been described between the fundus and the duodenum (approximately 6% of dichotomising afferents in mice (Zhong et al., 2008)).

Future work could assess molecules with the potential of reversing peripheral or central sensitisation once it has occurred. For example, the resolvin RvD2 reverses the sensitisation of TRPV1 and post-inflammatory colorectal hypersensitivity in rats (Perna et al., 2020). Similarly, resolvins could be tested in animal models of chronic cross-organ visceral sensitisation. The reversal of visceral hypersensitivity has also been demonstrated in rats using a proprietary combination of peppermint and caraway oils (Menthacarin®), with a possible role for mycobiome modulation in this phenomenon (Botschuijver et al., 2018). The role of the gut microbiota in visceral hypersensitivity and cross-organ sensitisation

should therefore be investigated, with the potential to identify anti-nociceptive properties linked to certain microbial species or compounds.

Translational research

Local immune activation following the application of food antigens in the duodenum of FD patients (Van den Houte et al., 2022) or the colon of IBS patients (Aguilera-Lizarraga et al., 2019) is increasingly described. The mechanisms involved in the local activation of mast cells are unknown, however, but seem to be IgE-independent (Park and Camilleri, 2006). Mas-related G protein-coupled receptor X2 (MRGPRX2, encoded by the *MRGPRX2* gene), specifically expressed in mast cells, has been implicated in pseudoallergies. Mast cell activation and degranulation mediated by MRGPRX2 are paramount in non-IgE-mediated drug reactions (McNeil et al., 2015). A subset of IBS patients (approximately one-third) have increased immune activation in the colon descendens; a 10.7-fold increase in *MRGPRX2* gene expression was found in colonic samples of those patients (Aguilera-Lizarraga et al., 2019). In contrast, FD patients have increased duodenal mastocytosis (Walker et al., 2009, Vanheel et al., 2014) and an altered duodenal barrier on confocal laser endomicroscopy (Nojkov et al., 2020). Furthermore, the expression of MRGPRX2 is increased in patients with chronic moderate/severe unexplained GI symptoms (Butuci et al., 2021). All those elements suggest that MRGPRX2 could be involved in symptom generation in FD patients. The role of pseudo-allergic reactions following the ingestion of food antigens in the generation of symptoms of both the upper and lower GI tracts in animal models of FD-IBS overlap and patients with FD-IBS overlap could, therefore, be investigated.

The immune system in the gut embraces the immune cells in the lamina propria of the intestinal mucosa and the gut-associated lymphoid tissue (GALT). Dendritic cells present in the GALT (CD103⁺) constantly sample the content of the intestinal lumen and are responsible for the tolerance to food antigens and the response to intestinal pathogens. Antigenic stimulation of those cells induces the metabolism of *all-trans*-retinol (vitamin A) in retinoic acid by the enzyme retinaldehyde dehydrogenase 2 (RALDH2) (Iwata et al., 2004). Retinoic acid induces the expression of the integrin $\alpha 4\beta 7$ and the C-C chemokine receptor type 9 (CCR9) on a subset of circulating T cells. Those activated $\alpha 4\beta 7^+$ T lymphocytes

have, therefore, a gut tropism. Indeed, this integrin specifically binds to the mucosal vascular addressin cell adhesion molecule (MAdCAM)-1, which is mostly expressed on endothelial cells in the GI tract (Briskin et al., 1997). This mechanism is unique to the gut and permits an intestinal immune response independently of the systemic response. Patients with FD have increased levels of circulating gut-homing ($CD4^+ \alpha 4\beta 7^+ CCR9^+$) T lymphocytes and inflammatory cytokines (TNF α , IL-10 and IL-1 β) (Liebregts et al., 2011). Both levels were correlated with symptom severity (pain, nausea and vomiting) and delayed GE (Liebregts et al., 2011). Furthermore, another study described increased circulating $\alpha 4\beta 7^+$ gut-homing T cells in FD and IBS patients (Burns et al., 2019). However, whether immune activation could occur at different sites (upper GI, lower GI or both) depending on the pathology involved (FD, IBS or FD+IBS overlap, respectively) is unknown. The levels of $\alpha 4\beta 7^+$ gut-homing T lymphocytes could be assessed in animal models of FD-IBS overlap and patients with FD alone, IBS alone and FD-IBS overlap to evaluate their implication in symptom generation. The effect of vedolizumab (Entyvio®), an anti- $\alpha 4\beta 7$ integrin antibody, could also be assessed experimentally in rodent models. To note, another protein, the G protein-coupled receptor 15 (GPR15), a chemoattractant receptor, is also involved in the homing of T lymphocytes to the colon (Kim et al., 2013).

The gut microbiome is all the microorganisms present in the GI tract, including bacteria, yeast, and viruses. By contrast, the gut microbiota is limited to the 3.9×10^{13} bacteria, with four main phyla (*Firmicutes*, *Bacteroidetes*, *Actinobacteria*, and *Proteobacteria*). The ratio of bacteria to human cells is 1:1 (Sender et al., 2016), but the human gut microbiota totalises 100 times as many genes as the human genome (Gill et al., 2006). The gut microbiota's gene content, called the metagenome, enriches the metabolic functions of the human organism (the complete set of metabolites being named the metabolome) and is involved in its homeostasis (Fan and Pedersen, 2021). Its composition is influenced by diet, physical activity, antibiotic usage, and host genetics, among other things (Manor et al., 2020). Dysbiosis involving the duodenal mucosa-associated microbiota is associated with dyspeptic symptoms in FD patients (Shanahan et al., 2022). The role of alterations of the colonic microbiota in symptom generation in FD patients and the possibility of specific gut dysbiosis in patients with FD-IBS overlap compared to patients with FD alone and IBS alone could be investigated. Similarly,

the role of gut microbiota alterations in other overlapping conditions in FD patients could be assessed.

12.3. Concluding remarks

The study of comorbidities and overlap syndromes in FD, and more generally DBGI, is a growing field of research involving numerous perspectives. Overlap syndromes and association with comorbidities in FD patients are the norm rather than an exception. Population-based studies could identify distinct patient cohorts in the future, and prospective trials could assess causal relationships in their pathogenesis. New therapeutic approaches taking into account comorbidities and overlap syndromes in the disorder could be evaluated. New and innovative animal models are also needed.



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Résumé substantiel en français – Executive summary in French

Les comorbidités et syndromes de chevauchement associés à la dyspepsie fonctionnelle sont peu étudiés. La dyspepsie fonctionnelle est le prototype des troubles fonctionnels gastro-duodénaux et est définie par quatre symptômes cardinaux: pesanteur épigastrique post-prandiale, satiété précoce, douleur épigastrique et/ou brûlure épigastrique. Un ralentissement de la vidange gastrique et/ou une hypersensibilité gastrique sont retrouvés chez certains patients. Les troubles fonctionnels digestifs, désormais appelés troubles des interactions intestin-cerveau, sont fréquemment associés à des comorbidités organiques ou psychologiques ainsi qu'à d'autres troubles fonctionnels, digestifs ou non ; on parle alors de syndromes de chevauchement. La maladie est connue pour être fréquemment associée au reflux gastro-oesophagien et au syndrome de l'intestin irritable, le prototype des troubles des interactions intestin-cerveau, notamment.

Le but de nos travaux est de faire le point sur les connaissances actuelles sur le sujet, d'évaluer différentes comorbidités et syndromes de chevauchement dans la dyspepsie fonctionnelle, et d'explorer les mécanismes physiopathologiques impliqués tant chez l'homme que chez l'animal.

Une revue systématique a permis de synthétiser les connaissances actuelles sur les comorbidités et les syndromes de chevauchement dans la dyspepsie fonctionnelle. Nous avons pour cela effectué une revue de la littérature à l'aide de MEDLINE (PubMed®) jusqu'en février 2022 : 5.131 références ont été identifiées, dont 250 ont été conservées pour analyse. Les différentes comorbidités mises en évidence ont été classées en 4 catégories : maladies organiques (gastrite à *Helicobacter pylori*, diabète sucré, intolérance au lactose...), autres troubles gastro-intestinaux fonctionnels (reflux gastro-oesophagien, syndrome de l'intestin irritable...), syndromes somatiques fonctionnels non gastro-intestinaux (syndrome de fatigue chronique, migraine...) et facteurs psychologiques (anxiété, dépression, troubles du sommeil, troubles alimentaires...).

Parmi les comorbidités associées à la dyspepsie fonctionnelle qui ont été révélées dans notre revue systématique, nous avons considéré les troubles du

sommeil comme particulièrement intéressants pour étudier les liens de causalité entre certaines comorbidités et la maladie. De plus, cela nous a permis de mieux caractériser le sommeil altéré dans la dyspepsie fonctionnelle et d'évaluer les facteurs influençant la qualité de vie dans cette maladie. Nous sommes partis d'une population de 1.220 patients référés pour des troubles fonctionnels gastro-intestinaux dans un seul centre de soins tertiaires, parmi lesquels 355 patients atteints de dyspepsie fonctionnelle selon les critères de Rome IV ont été gardés pour analyse. Les résultats d'un questionnaire auto-administré ont permis d'étudier le sommeil (qualité du sommeil et insomnie), la gravité des symptômes dyspeptiques, la qualité de vie et les niveaux d'anxiété et de dépression. Nous avons montré que 18,6 % des patients dyspeptiques affichaient une qualité du sommeil normale alors que 81,4 % avaient une qualité du sommeil altérée. De plus, une insomnie était présente chez 60,6% d'entre eux. Les patients atteints de dyspepsie fonctionnelle et souffrant également de troubles du sommeil étaient plus âgés, avaient une qualité de vie plus altérée, une plus grande sévérité de leurs symptômes et des scores d'anxiété et de dépression plus élevés. Nous avons trouvé une corrélation entre la qualité du sommeil et la qualité de vie. Enfin, les facteurs prédictifs indépendants d'une mauvaise qualité du sommeil dans cette maladie étaient l'âge, le niveau de dépression et la sévérité des symptômes dyspeptiques.

La dyspepsie fonctionnelle et le syndrome des nausées et vomissements chroniques sont des entités définies par des groupes de symptômes. Les critères utilisés pour leurs définitions sont donc d'une importance primordiale. Même si les nausées et les vomissements sont fréquemment rapportés par les patients dyspeptiques, les critères de Rome successifs ont progressivement modifié la place de ces symptômes dans le diagnostic de la dyspepsie fonctionnelle, les critères de Rome IV fusionnant les troubles de nausées et vomissements en une seule entité appelée syndrome des nausées et vomissements chroniques. Nous avons voulu questionner la place des symptômes de nausées et de vomissements dans le diagnostic de dyspepsie fonctionnelle. Pour cela, nous sommes partis d'une population de 3.471 patients consécutifs atteints de dyspepsie investiguée, parmi lesquels 1.188 patients atteints de dyspepsie fonctionnelle et/ou de syndrome des nausées et vomissements chroniques selon les critères de Rome IV ont été gardés pour analyse. Les résultats d'un questionnaire auto-administré ont permis d'étudier le sommeil, la gravité des symptômes dyspeptiques, la qualité de

vie, les niveaux d'anxiété-dépression ainsi que la fréquence de 8 symptômes digestifs évaluée de manière prospective à l'aide d'une échelle de Likert en 5 points durant les 15 jours précédents. Nous avons montré que les nausées, et dans une moindre mesure les vomissements, sont fréquents chez les patients consultant pour des troubles dyspeptiques, que le syndrome des nausées et vomissements chroniques survient en chevauchement avec une dyspepsie fonctionnelle dans 73,2% des cas, alors que la dyspepsie fonctionnelle survient en chevauchement avec un syndrome des nausées et vomissements chroniques dans 37,6% des cas. Les patients avec un chevauchement entre les 2 entités avaient une qualité de vie plus altérée que ceux avec l'un ou l'autre diagnostic seul. Tous les symptômes étaient au moins aussi fréquents chez les patients avec chevauchement entre dyspepsie fonctionnelle et syndrome des nausées et vomissements chroniques que chez ceux avec dyspepsie fonctionnelle seule. Nous avons donc conclu que le chevauchement entre la dyspepsie fonctionnelle et le syndrome des nausées et vomissements chroniques est fréquent et que les patients qui en sont atteints ont les caractéristiques des patients dyspeptiques seuls mais avec une gravité plus élevée de leur maladie.

Les mécanismes physiopathologiques impliqués dans la dyspepsie fonctionnelle sont incomplètement compris. En particulier, une altération de l'accommodation gastrique, un retard de vidange gastrique et une hypersensibilité à la distension gastrique semblent être en cause. Les associations entre symptômes, qualité de vie et vidange gastrique dans la dyspepsie sont inconstants dans la littérature. Nous avons donc décidé de réaliser une étude mécanistique pour évaluer le lien entre un mécanisme physiopathologique et les symptômes présentés par les patients. Il s'agit d'un travail rétrospectif sur 198 patients consécutifs présentant des symptômes de type gastroparésie et référés pour un test de vidange gastrique. La dyspepsie était définie en dehors des critères de Rome et la vidange gastrique mesurée par un test respiratoire à l'acide octanoïque marqué au carbone 13 durant plus de 6 heures. Un questionnaire auto-administré était également rempli par les patients afin d'évaluer leurs symptômes gastro-intestinaux sur une échelle de Likert à 5 points et leur qualité de vie. Nous avons trouvé que 45% des patients avaient une vidange gastrique retardée (temps de demi-vidange supérieur à 166 minutes lorsqu'il était évalué sur 6 à 8 heures) et qu'il n'y avait aucune différence concernant les symptômes ou la qualité de vie entre les patients avec et sans retard de vidange gastrique. Par

contre, les patients souffrant d'un retard sévère de leur vidange gastrique (temps de demi-vidange supérieur à 200 minutes) présentaient une pesanteur épigastrique post-prandiale accrue, plus de douleurs abdominales, de ballonnements et de satiété précoce, ainsi qu'une qualité de vie plus altérée. L'association avec les symptômes et la qualité de vie n'était plus observée si le calcul de la vidange gastrique était limité aux 4 premières heures de mesure. Nous avons donc conclu qu'il n'y a pas d'association entre les symptômes, la qualité de vie et la vidange gastrique dans une population dyspeptique globale mais qu'il existe une association entre eux dans le sous-groupe de patients présentant un retard sévère de la vidange gastrique. Enfin, une mesure de la vidange gastrique sur 8 heures devrait être recommandée lorsque la méthode de test respiratoire à l'acide octanoïque est utilisée.

Les autres troubles associés à la dyspepsie fonctionnelle peuvent provenir de différents organes. Le côlon, l'estomac et la vessie sont les trois principaux organes abdominaux partagés par les deux sexes chez l'Homme. L'interaction entre la vessie et le côlon est bien décrite. En effet, la dyspepsie fonctionnelle et le syndrome de vessie douloureuse sont tous deux bien connus pour chevaucher avec le syndrome de l'intestin irritable. Cependant, on ne savait pas si la dyspepsie fonctionnelle chevauchait le syndrome de vessie douloureuse. Nous sommes donc partis d'une population de 1,650 patients consécutifs présentant des symptômes dyspeptiques investigués, dont 1,453 ont été gardés pour analyse, parmi lesquels 892 souffraient de dyspepsie fonctionnelle. La dyspepsie fonctionnelle et le syndrome de l'intestin irritable étaient définis par les critères de Rome III ou IV alors que le syndrome de vessie douloureuse l'était selon les critères ESSIC de 2008. Nous avons trouvé que le syndrome de vessie douloureuse est présent chez 26,9 % des patients atteints de dyspepsie fonctionnelle (22,2 % des patients atteints de dyspepsie fonctionnelle seule contre 36,4 % des patients atteints d'un chevauchement entre dyspepsie fonctionnelle et syndrome de l'intestin irritable). Le chevauchement entre dyspepsie fonctionnelle et syndrome de vessie douloureuse est associé à des niveaux plus élevés de sévérité des symptômes dyspeptiques, d'anxiété, de dépression et d'insomnie, et à une qualité de vie plus altérée. Les mêmes conclusions mais avec des résultats encore plus prononcés étaient retrouvées en cas de chevauchement avec le syndrome de l'intestin irritable. Nous en avons conclu que le syndrome de vessie douloureuse est fréquent parmi les patients atteints de dyspepsie fonctionnelle et qu'il doit être

évalué de la même manière que les autres comorbidités que sont le reflux gastro-œsophagien et le syndrome de l'intestin irritable chez ces patients.

Des travaux antérieurs ont étudié les interactions vessie-côlon. En effet, le syndrome de l'intestin irritable et le syndrome de vessie douloureuse se chevauchent fréquemment et les deux maladies sont caractérisées par une hypersensibilité viscérale. Étant donné que les organes pelviens partagent des voies sensorielles communes, il était probable que ces syndromes impliquent une sensibilisation croisée entre la vessie et le côlon, mais la physiopathologie précise restait mal comprise. Un nouveau modèle de sensibilisation viscérale inter-organes entre la vessie et le côlon avait été mis au point chez la souris. Les injections intra-vésicales d'acide acétique induisaient une hypersensibilité à la distension colo-rectale de manière durable. La sensibilisation croisée vessie-côlon était médiée dans ce modèle par les interactions neuro-gliales, la phosphorylation de la mitogen-activated protein (MAP) kinase p38 et le récepteur de la neurokinine 1 (NK1). Nous en avons conclu que les interactions impliquant la microglie étaient centrales dans ce processus.

Le chevauchement entre la dyspepsie fonctionnelle et le syndrome de l'intestin irritable est fréquent comme nous l'avons vu dans nos précédents travaux. Les deux troubles sont caractérisés par une hypersensibilité viscérale chez une partie des patients. Une sensibilisation viscérale inter-organes a été rapportée entre des organes partageant des voies sensorielles communes comme nous l'avons montré dans les travaux sur les interactions vessie-côlon. Étant donné que les mécanismes physiopathologiques du chevauchement entre dyspepsie fonctionnelle et syndrome de l'intestin irritable restent flous, nous avons décidé d'étudier la possibilité d'une sensibilisation croisée côlon-estomac puisque l'estomac et le côlon proximal sont tous deux innervés par le nerf vague chez le rat.

Nous avons induit une colite chimique à l'acide trinitrobenzène sulfonique (TNBS) pour la sensibilisation du côlon à l'estomac chez des rats Sprague-Dawley mâles âgés de 7 semaines. Les sensibilités gastrique et colorectale ont été évaluées chez les rats sédatisés par phénobarbital en mesurant les variations de pression artérielle mesurées au niveau de l'artère carotide gauche lors de distensions gastriques et colorectales isobares respectivement. Les autres paramètres étudiés étaient l'inflammation tissulaire (myéloperoxydase), la perméabilité tissulaire (chambres de Ussing avec les colorants fluorescents jaune

Résumé substantiel

Lucifer et Alexa Fluor™ 680), l'inflammation systémique (dosage multiplex de cytokines), l'inflammation au niveau de la moelle épinière (PCR quantitative) et l'expression des récepteurs NK1 et de la MAPK-p38 phosphorylée dans la moelle épinière (western blot). Nous avons développé un nouveau modèle de sensibilisation viscérale inter-organes entre le côlon et l'estomac chez le rat, une colite induite par le TNBS induisant des hypersensibilités aux distensions colorectale et gastrique soutenues au jour 7. Cette hypersensibilité gastrique mesurée 1 semaine après la colite chimique est indépendante de la réaction inflammatoire et est prévenue par l'administration centrale de minocycline, un inhibiteur de la microglie. L'expression de la MAPK-p38 phosphorylée dans la moelle épinière est majorée au 2^{ème} jour après l'induction de la colite chimique, ce qui suggère que cette voie est impliquée dans le développement de l'hypersensibilité viscérale croisée. Nous avons conclu que les interactions avec la microglie sont centrales dans la sensibilisation croisée côlon-estomac. Ce nouveau modèle peut être utilisé comme modèle préclinique de chevauchement entre la dyspepsie fonctionnelle et le syndrome de l'intestin irritable.

En conclusion, l'étude des comorbidités et des syndromes de chevauchement dans la dyspepsie fonctionnelle, et plus généralement dans les troubles des interactions intestin-cerveau, est un domaine de recherche en pleine expansion avec de nombreuses perspectives. Des cohortes de patients distinctes pourraient être identifiées dans des études en population incluant des sujets sains, et des relations causales impliquées dans leur pathogenèse pourraient être identifiées dans des essais prospectifs.



Curriculum vitæ

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Fabien WUESTENBERGHS

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Positions

- 2007-2010: internships during my studies
- 2010-2016: residency
- 2016-: specialist in gastroenterology
(sub-specialties: neurogastroenterology & proctology)
 - 2016-2019: fellow at CHU UCL Namur 
 - 2019-2023: deputy head of clinic
at CHU UCL Namur 
- Abroad:
 - 2017: internship in the Digestive Physiology department (CHU Rouen )
 - 2017-2022: part-time doctoral specialist (host laboratory: UMR 1073, UNIROUEN )



Diplomas

- 2010: Medical doctor, UCLouvain 
- 2015: Diploma « Etudes des maladies inflammatoires chroniques intestinales », Université Lille2 
- 2016: Master's degree in gastroenterology, UCLouvain 

Curriculum vitæ

- 2016: European Board of Gastroenterology & Hepatology Examination 
- 2016: Diploma « Pathologies Fonctionnelles Digestives », Université Lyon1 
- 2016: Diploma « Proctologie », Université Rennes1 
- 2016: Certificate in radiation protection, UCLouvain 
- 2017: Diploma in statistics from the « CESAM » (Centre d'Enseignement de la Statistique à la Santé Publique, à la Médecine et à la Biologie), Paris VI, Sorbonne-Universités 
- 2017: Diploma « Méthodes en Recherche Clinique », Université Bordeaux2 
- 2018: Certificate « Science et médecine des animaux de laboratoire » (FELASA C), UCLouvain 
- 2019: Diploma « Pelvi-périnéologie », Université Toulouse III - Paul Sabatier 
- 2020: Diploma « Pédagogie médicale », Normandie Université, UNIROUEN 
- 2021: Master of Science in Clinical Trials (Online learning) (MScCT), University of Edinburgh 

Research

- 21 publications including 15 original articles
 - *h*-index = 5 & 122 citations as of March 13, 2023 [Source: Scopus ]
- Reviewing of articles for scientific journals:
 - see Web of Science™ 
<https://www.webofscience.com/wos/author/record/921560>
- Participation to expert groups:
 - Belgian IBS consensus group (2020-2021)
- Clinical trials:
 - Sub-investigator for the « LPDS/Itopride study » from KULeuven (2014-2016)
 - Certificate in “Good Clinical Practice” – ICH-GCP (validity → January 30, 2024)

Responsibilities in scientific societies

- Member of the scientific committee of the Société Royale Belge de Gastro-Entérologie (SRBGE)  (2017-)
- Member of the governing board of the Belgian Society of Neurogastroenterology and Motility (BSNM)  (2023-)

Teaching

- 4 hours of teaching for the “Master de spécialisation en gastro-entérologie” (GAEN2MC, UCLouvain) (2020-2022)
- Internship supervisor in proctology (as part of the Proctology Diploma at Université Rennes1 )
- Supervision of 2 Master's research dissertations as promoter (gastro-enterology)
 - Influence of general anaesthesia on completion rate of capsule endoscopy in real life: a retrospective monocentric study (2017-2019, UCLouvain)
 - Optimal duration of the stabilization period during 3D-HDAM: influence on resting pressures and detection of other events (2021-2022, ULg)
- Supervision of 1 Master's dissertations as promoter (pharmacy)
 - Rôle du pharmacien d'officine dans la prise en charge du syndrome de l'intestin irritable (2022-, UNamur-UCLouvain)
- Co-organisation of 2 regional symposia  (2017 & 2018)



Publications, dissemination and training

Publications and communications linked with the work of this PhD thesis appear in bold.

Publications in journals with peer review 

Original articles

1. **Fabien Wuestenberghs**, Mathilde Juge, Chloé Melchior, Charlotte Desprez, Anne-Marie Leroi, Guillaume Gourcerol. Association between symptoms, quality of life and gastric emptying in dyspeptic patients. *Journal of Neurogastroenterology and Motility* 2019 ; 25 (4) : 534-543. <https://doi.org/10.5056/jnm19060f>
2. Charlotte Desprez, Chloé Melchior, **Fabien Wuestenberghs**, Alberto Zalar, Jérémie Jacques, Anne-Marie Leroi, Guillaume Gourcerol. Pyloric distensibility measurement predicts symptomatic response to intrapyloric botulinum toxin injection. *Gastrointestinal Endoscopy* 2019 ; 90 (5) : 754-760. <https://doi.org/10.1016/j.gie.2019.04.228>
3. Charlotte Desprez, Chloé Melchior, **Fabien Wuestenberghs**, Emmanuel Huet, Alberto Zalar, Jérémie Jacques, Anne-Marie Leroi, Guillaume Gourcerol. Pyloric distensibility measurement after gastric surgery: which surgeries are associated with pylorospasm? *Neurogastroenterology & Motility* 2020 ; 32 (5) : e13790. <https://doi.org/10.1111/nmo.13790>
4. Julien Favresse, Caroline Fervaille, **Fabien Wuestenberghs**, Bernard Chatelain, François Mullier, Hugues Jacqmin. Utility of the XN-1000 Research Mode for Leukocytes Counting in Ascitic and Pleural Fluids. *International Journal of Laboratory Hematology* 2020 ; 42 (3) : e92-e95. <https://doi.org/10.1111/ijlh.13128>
5. Julien Favresse, Lidvine Bolland, Marie Schellen, Caroline Fervaille, **Fabien Wuestenberghs**, Alessandra Camboni, Bernard Chatelain, François Mullier, Jean-Philippe Defour, Hugues Jacqmin. Two-site evaluation of a new workflow for the detection of malignant cells on the Sysmex XN-1000 body fluid analyzer. *International Journal of Laboratory Hematology* 2020 ; 42 (5) : 544-551. <https://www.doi.org/10.1111/ijlh.13187>
6. Chloé Melchior, Charlotte Desprez, **Fabien Wuestenberghs**, Anne-Marie Leroi, Antoine Lemaire and Guillaume Goucerol. Impact of Opioid Consumption in Patients With Functional Gastrointestinal Disorders. *Frontiers in Pharmacology* 2020 ; 11 : 596467 (eCollection 2020) <https://doi.org/10.3389/fphar.2020.596467>

7. Karen Van den Houte, Florencia Carbone, Nick Goelen, Jolien Schol, Imke Masuy, Joris Arts, Philip Caenepeel, Dirk Staessen, Philippe Vergauwe, Guy Van Roey, Pascale Latour, Hubert Piessevaux, Philippe Maldague, Ariane Gerkens, **Fabien Wuestenberghs**, Alain Vandenberghe, Jan Tack. Effects of Rome IV Definitions of Functional Dyspepsia Subgroups in Secondary Care. *Clinical Gastroenterology and Hepatology* 2021 ; 19 (8) : 1620-1626. <https://doi.org/10.1016/j.cgh.2020.06.043>
8. Sofya Latrache, Chloe Melchior, Charlotte Desprez, Sabrina Sidali, Julien Rector, Olivier Touchais, Elise van der Eecken, **Fabien Wuestenberghs**, Cloe Charpentier, Anne Marie Leroi, Guillaume Gourcerol. Is it necessary to perform a morphological assessment for an esophageal motility disorder? A retrospective descriptive study. *Clinics and Research in Hepatology and Gastroenterology* 2021 ; 45 (6) : 101633. <https://doi.org/10.1016/j.clinre.2021.101633>
9. Nicolas Richard, Charlotte Desprez, **Fabien Wuestenberghs**, Anne-Marie Leroi, Guillaume Gourcerol, Chloé Melchior. The effectiveness of rotating versus single course antibiotics for small intestinal bacterial overgrowth. *United European Gastroenterology Journal* 2021 ; 9 (6) : 645-654. <https://doi.org/10.1002/ueg2.12116>
10. Guillaume Gourcerol, Chloé Melchior, **Fabien Wuestenberghs**, Charlotte Desprez, Gaëtan Prevost, Julien Grosjean, Anne-Marie Leroi, Marie-Pierre Tavolacci. Delayed gastric emptying as an independent predictor of mortality in gastroparesis. *Alimentary Pharmacology & Therapeutics* 2022 ; 55 (7) : 867-875. <https://doi.org/10.1111/apt.16827>
11. **Fabien Wuestenberghs**, Chloé Melchior, Charlotte Desprez, Anne-Marie Leroi, Marie Netchitailo, Guillaume Gourcerol. Sleep Quality and Insomnia Are Associated With Quality of Life in Functional Dyspepsia. *Frontiers in Neuroscience* 2022 ; 16 : 829916. <https://doi.org/10.3389/fnins.2022.829916>
12. Florencia Carbone, Alain Vandenberghe, Lieselot Holvoet, Hubert Piessevaux, Joris Arts, Philippe Caenepeel, Dirk Staessen, Philippe Vergauwe, Philippe Maldague, Thierry De Ronde, **Fabien Wuestenberghs**, Vincent Lamy, Véronique Lefebvre, Pascale Latour, Tim Vanuytsel, Michael Jones, Jan Tack. A Double-blind randomized, multicenter, placebo-controlled study of itopride in functional dyspepsia postprandial distress syndrome. *Neurogastroenterology & Motility* 2022 ; 34 (8) : e14337. <https://doi.org/10.1111/nmo.14337>
13. Colin Dumont, **Fabien Wuestenberghs**, Nicolas Lanthier, Hubert Piessevaux, Géraldine Dahlqvist. Malnutrition is highly prevalent in hospitalized cirrhotic patients and associates with a poor outcome. *Acta*

- Gastro-Enterologica Belgica* 2022 ; 85 : 311-319.
<https://doi.org/10.51821/85.2.9016>
14. Fabien Wuestenberghs, Maximilien Baron, Chloé Melchior, Charlotte Desprez, Jean-Nicolas Cornu, Anne-Marie Leroi, Guillaume Gourcerol. Overlaps with bladder pain syndrome and irritable bowel syndrome are associated with higher symptom burden and reduced quality of life in functional dyspepsia. *Neurogastroenterology & Motility* 2022 ; 34 (11) : e14414. <https://doi.org/10.1111/nmo.14414>
 15. Karim Atmani, Fabien Wuestenberghs, Maximilien Baron, Illona Bouleté, Charlene Guérin, Wafa Bahlouli, David Vaudry, Jean Claude do Rego, Jean-Nicolas Cornu, Anne-Marie Leroi, Moïse Coëffier, Mathieu Meleine and Guillaume Gourcerol. Bladder-colon chronic cross-sensitization involves neuro-glial pathways in male mice. *World Journal of Gastroenterology* 2022 ; 28 (48) : 6935-6949.
<https://doi.org/10.3748/wjg.v28.i48.6935>

Other publications

1. Fabien Wuestenberghs, Patrick Druez. Unusual Esophageal Foreign Body. *Gastroenterology* 2016 ; 151 (4) : 603-604.
<https://doi.org/10.1053/j.gastro.2016.06.007>
2. Fabien Wuestenberghs, Nathalie Pirson, Pierre Bulpa, Caroline Fervaille, Alain Dive. Iatrogenic cerebral air embolism revealing an atrial-esophageal fistula. *Internal and Emergency Medicine* 2017 ; 12 (5) : 715.
<https://doi.org/10.1007/s11739-016-1561-0>
3. Fabien Wuestenberghs, Guillaume Gourcerol, Pierre Déchelotte, Moïse Coëffier. *Akkermansia muciniphila* in functional GI disorders: good rather than evil? *The Journal of Clinical Investigation* 2018 (E-letter)
<https://www.jci.org/eletters/view/92390#sec1>
4. Fabien Wuestenberghs and Guillaume Gourcerol. Pyloric distensibility in health and disease. *American Journal of Physiology-Gastrointestinal and Liver Physiology* 2021 ; 321 (2) : G133-G138.
<https://doi.org/10.1152/ajpgi.00460.2020>
5. Fabien Wuestenberghs, Guillaume Gourcerol. Editorial: on the road towards treatment of gastroparesis-accelerating but do we get closer? *Alimentary Pharmacology & Therapeutics* 2021 ; 54 (2) : 183-184.
<https://doi.org/10.1111/apt.16375>
6. Sébastien Kindt, Hubert Louis, Heiko De Schepper, Joris Arts, Philip Caenepeel, Dany De Looze, Arianne Gerkens, Tom Holvoet, Pascale Latour, Tania Mahler, Faddy Mokaddem, Sarah Nullens, Hubert Piessevaux, Pieter Poortmans, Gertjan Rasschaert, Magali Surmont, Vafa

Haydeh, Kathleen Van Malderen, Tim Vanuytsel, **Fabien Wuestenberghs**, Jan Tack. Belgian consensus on irritable bowel syndrome. *Acta Gastro-Enterologica Belgica* 2022 ; 85 : 360-382.
<https://doi.org/10.51821/85.2.10100>

Conference papers

Poster presentations

- **Fabien Wuestenberghs**, Nathalie Pirson, Caroline Fervaille, Pierre Bulpa, Isabelle Michaux, Alain Dive. Cerebral Air Embolism after Gastroscopy. 33th Annual Meeting of the SIZ (Belgian Society of Intensive Care Medicine), Living Tomorrow, Brussels, Belgium, June 14, 2013.
<http://dx.doi.org/10.13140/RG.2.2.15570.96968>
- **Fabien Wuestenberghs**, Nicolas Lanthier, Hubert Piessevaux, Géraldine Dahlqvist. Su1522 Impact of Nutritional Status on Cirrhotic Inpatients' Prognosis: A Retrospective Monocentric Study. *Gastroenterology* 2016 ; 150 (4), Supplement 1 : S1120, Digestive Disease Week, San Diego, USA, May 22, 2016 [abstract Su1522] [http://dx.doi.org/10.1016/S0016-5085\(16\)33778-7](http://dx.doi.org/10.1016/S0016-5085(16)33778-7)
- **Fabien Wuestenberghs**, Chloé Melchior, Anne-Marie Leroi, Guillaume Gourcerol. Provocative testing increases the diagnostic yield of high resolution oesophageal manometry in patients with oesophageal diverticula. *Neurogastroenterology & Motility* 2017 ; 29 (S2), 103-103. Special Issue: Abstract Supplement for NeuroGASTRO 2017 Congress, NeuroGASTRO, Cork, Ireland, August 24-26, 2017 [abstract 208] <https://doi.org/10.1111/nmo.13180>
- **Fabien Wuestenberghs**, Chloé A. Melchior, Anne-Marie Leroi, Guillaume Gourcerol. P1175 Provocative testing increases the diagnostic yield of high resolution oesophageal manometry in patients with oesophageal diverticula. in UEG Week 2017 Poster Presentations (Abstract book). *UEG Journal* 2017 ; 5 (5_suppl) : A161-A836, UEG Week, Barcelona, Spain, October 28 - November 1, 2017.
<https://doi.org/10.1177/2050640617725676>
- Chloé Melchior, Charlotte Desprez, **Fabien Wuestenberghs**, Anne-Marie Leroi, Antoine Lemaire, Guillaume Gourcerol. Opioids consumption in patients referred for functional gastro-intestinal disorders. *Neurogastroenterology & Motility* 2019 ; 31 (S4) : e13671. Special issue: Abstract Supplement for NeuroGASTRO 2019 Congress, NeuroGASTRO, Lisbon, Portugal, September 5-7, 2019 [abstract 260] <https://doi.org/10.1111/nmo.13671>

- Olivier De Ronde, Thierry De Ronde, **Fabien Wuestenberghs**. Same day propofol sedation does not impair the completion rate of capsule endoscopy, *Acta Gastroenterologica Belgica* 2020 ; 83 (1) : G21, Belgian Week of Gastroenterology, Antwerpen, Belgium, March 4-6, 2020 [abstract 46, BSGIE e-poster] <https://www.bwge.be/wp-content/uploads/2020/01/Programme BWG 2020 web.pdf>
- **Fabien Wuestenberghs, Chloé Melchior, Charlotte Desprez, Anne-Marie Leroi, Guillaume Gourcerol**. P.488 Intérêt de demander l'effet de bains d'eau chaude sur les vomissements, e-JFHOD, virtual, June 25-28, 2020 [abstract n°000250] <https://www.snfge.org/resumes-2020/000250>
- Nicolas Richard, Charlotte Desprez, Fabien Wuestenberghs, Anne-Marie Leroi, Guillaume Gourcerol, Chloé Melchior. P0256 Small intestinal bacterial overgrowth remission and symptoms improvement after antibiotic treatment: a French retrospective comparative study. in UEG Week 2020 Poster Presentations (Abstract book). *UEG Journal* 2020 ; 8 (S8) : 144-887, UEG Week, virtual, October 11-13, 2020. <https://doi.org/10.1177/2050640620927345>
- **Fabien Wuestenberghs, Chloé Melchior, Charlotte Desprez, Anne-Marie Leroi, Marie Netchitailo, Guillaume Gourcerol**. Sa391 Sleep disorders are associated with a lower quality of life in functional dyspepsia. *Gastroenterology* 2021 ; 160 (6) : S488. Digestive Disease Week, virtual, May 21-23, 2021 [abstract Sa391] [https://doi.org/10.1016/S0016-5085\(21\)01873-4](https://doi.org/10.1016/S0016-5085(21)01873-4)
- **Fabien Wuestenberghs, Maria P. Eugenicos**. Reporting of comorbidities and overlap syndromes in functional dyspepsia trials: a systematic review of RCTs over 15 years. *Neurogastroenterology & Motility* 2021 ; 33 (S2) : e14244. Special issue: Abstract Supplement for NeuroGASTRO 2021 Congress, NeuroGASTRO, virtual, September 2-4, 2021 [abstract NGS15375-93] <https://doi.org/10.1111/nmo.14244>
- **Fabien Wuestenberghs, Chloé Melchior, Charlotte Desprez, Anne-Marie Leroi, Marie Netchitailo, Guillaume Gourcerol**. Sleep quality and insomnia are associated with a lower quality of life in functional dyspepsia. *Neurogastroenterology & Motility* 2021 ; 33 (S2) : e14244. Special issue: Abstract Supplement for NeuroGASTRO 2021 Congress, neuroGASTRO, virtual, September 2-4, 2021 [abstract NGS15372-90] <https://doi.org/10.1111/nmo.14244>
- **Fabien Wuestenberghs, Maria P. Eugenicos**. PWE-62 Reporting of comorbidities and overlap syndromes in functional dyspepsia: review of 15 years of RCTs. *Gut* 2021 ; 70 (Suppl 4) A174-A175, British Society of Gastroenterology's annual meeting, virtual, November 8-12, 2021

[abstract #534] <http://dx.doi.org/10.1136/gutjnl-2021-BSG.324>
<https://youtu.be/gPTJhXXR-84> [poster of distinction]

- **Fabien Wuestenberghs**, Chloé Melchior, Charlotte Desprez, Heithem Soliman, Anne-Marie Leroi, Guillaume Gourcerol. P0022 Prevalence and impact of migraine headaches in Rome IV-based functional dyspepsia. in UEG Week 2022 Poster Presentations (Abstract book). *UEG Journal* 2022 ; 10 (S8) : 473-1092, UEG Week, Vienna (and virtual), Austria, October 8-11, 2022 [abstract AS-UEG-2022-02097] <https://doi.org/10.1002/ueg2.12295>
- Paul Kisoka, **Fabien Wuestenberghs**, Edoenam Akpokavie, Guillaume Burnet, Nicolas De Suray, Milena Del Natale, Hossine Hassaini, Zaina Issa, Cristina Leu, Sergio Negrin Dastis, Alain Sibille, Philippe Warzée. Efficacy and safety of G-POEM in management of patients with refractory gastroparesis: about 10 cases. *Acta Gastroenterologica Belgica* 2023 ; 86 (1) : G24, Belgian Week of Gastroenterology, Antwerpen, Belgium, March 8-10, 2023 [abstract 77, BSGIE e-poster] <https://www.bwge.be/wp-content/uploads/programs/BWGE2023ProgramBSGIEThursdaySession.pdf>

Oral communications

- **Fabien Wuestenberghs**, Julien Depaus, Georgios Mavrogenis, Alain Sibille, Philippe Warzée. Systemic cat scratch disease mimicking lymphoma in a patient with Crohn's disease. *Acta Gastroenterologica Belgica* 2015 ; 78 (1) : C01, Belgian Week of Gastroenterology, Brussels, Belgium, February 25-28, 2015 https://www.bwge.be/wp-content/themes/Evento/pdf/Acta_Abstracts2015.pdf
- **Fabien Wuestenberghs**, Nicolas Lanthier, Hubert Piessevaux, Géraldine Dahlqvist. Impact of nutritional status on cirrhotic inpatients' prognosis: a retrospective monocentric study. *Acta Gastroenterologica Belgica* 2016 ; 79 (1) : A24, Belgian Week of Gastroenterology, Brussels, Belgium, February 25-28, 2015 <http://hdl.handle.net/2078.1/172411>
- Charlotte Desprez, Chloé Melchior, **Fabien Wuestenberghs**, Alberto Zalar, Jérémie Jacques, Anne-Marie Leroi, Guillaume Gourcerol. CO.114 La mesure de la distensibilité pylorique est-elle prédictive de la réponse symptomatique aux injections intrapyloriques de toxine botulique ? JFHOD, Paris, France, Marc 21-24, 2019 [abstract n°000561] <https://www.snfge.org/resumes-2019/000561>
- **Fabien Wuestenberghs**, Maximilien Baron, Chloé Melchior, Charlotte Desprez, Jean-Nicolas Cornu, Anne-Marie Leroi, Guillaume Gourcerol. Irritable bowel syndrome and bladder pain syndrome comorbidities are associated with altered quality of life, anxiety, depression and sleep in

- patients with functional dyspepsia. *Neurogastroenterology & Motility* 2019 ; 31 (S4) : e13671. Special issue: Abstract Supplement for NeuroGASTRO 2019 Congress, NeuroGASTRO, Lisbon, Portugal, September 5-7, 2019 [abstract 265] <https://doi.org/10.1111/nmo.13671>
- Chloé Melchior, Charlotte Desprez, **Fabien Wuestenberghs**, Anne-Marie Leroi, Antoine Lemaire, Guillaume Gourcerol. CO.026 Etat des lieux sur la consommation d'opioïdes dans une population de patients adressés pour troubles fonctionnels digestifs dans un centre tertiaire, e-JFHOD, virtual, June 25-28, 2020 [abstract n°000202] <https://www.snfge.org/resumes-2020/000202>
 - Chloé Melchior, Charlotte Desprez, **Fabien Wuestenberghs**, Anne-Marie Leroi, Guillaume Gourcerol. CO.027 Apport de la manométrie du grêle chez les malades présentant une suspicion clinique de pseudo-obstruction intestinale chronique (POIC), e-JFHOD, virtual, June 25-28, 2020 [abstract n°000301] <https://www.snfge.org/resumes-2020/000301>
 - Chloé Melchior, Charlotte Desprez, **Fabien Wuestenberghs**, G. Benjamin, Anne-Marie Leroi, Guillaume Gourcerol. CO.023 Comparaison de différentes antibiothérapies séquentielles dans la pullulation microbienne du grêle, e-JFHOD, virtual, June 25-28, 2020 [abstract n°000649] <https://www.snfge.org/resumes-2020/000649>
 - Guillaume Gourcerol, Chloé Melchior, **Fabien Wuestenberghs**, Charlotte Desprez, Gaëtan Prevost, Julien Grosjean, Anne-Marie Leroi, Marie-Pierre Tavalacci. CO.168 La gastroparésie est associée à une surmortalité : analyse à partir d'une cohorte de plus de 13000 patients.années, JFHOD, virtual, March 18-21, 2021 [abstract n°000503] <https://www.snfge.org/resumes-2021/000503>
 - **Fabien Wuestenberghs**, Chloé Melchior, Charlotte Desprez, Anne-Marie Leroi, Marie Netchitailo, Guillaume Gourcerol. CO.016 La qualité du sommeil et l'insomnie sont associées à la qualité de vie dans la dyspepsie fonctionnelle, JFHOD, virtual, March 18-21, 2021 [abstract n°000650] <https://www.snfge.org/resumes-2021/000650>
 - Guillaume Gourcerol, Chloé Melchior, **Fabien Wuestenberghs**, Charlotte Desprez, Gaëtan Prevost, Julien Grosjean, Anne-Marie Leroi, Marie-Pierre Tavalacci. OP003 Gastroparesis is associated with increased mortality: results from a cohort of more than 13 000 patients-year. in UEG Week 2021 Oral Presentations (Abstract book). *UEG Journal* 2021 ; 9 (S8) : 7-161, UEG Week, virtual, October 3-5, 2021 [abstract AS-UEG-2021-01785] <https://doi.org/10.1002/ueg2.12142>

Oral presentations

Oral communications

- **Fabien Wuestenberghs**, Maximilien Baron, Chloé Melchior, Charlotte Desprez, Jean-Nicolas Cornu, Anne-Marie Leroi, Guillaume Gourcerol. Irritable bowel syndrome and bladder pain syndrome comorbidities are associated with altered quality of life, anxiety, depression and sleep in patients with functional dyspepsia. *Neurogastroenterology & Motility* 2019 ; 31 (S4) : e13671. Special issue: Abstract Supplement for NeuroGASTRO 2019 Congress, NeuroGASTRO, Lisbon, Portugal, September 5-7, 2019 [abstract 265] <https://doi.org/10.1111/nmo.13671>
- **Fabien Wuestenberghs**, Chloé Melchior, Charlotte Desprez, Anne-Marie Leroi, Marie Netchitailo, Guillaume Gourcerol. CO.016 La qualité du sommeil et l'insomnie sont associées à la qualité de vie dans la dyspepsie fonctionnelle, JFHOD, virtual, March 18-21, 2021 [abstract n°000650] <https://www.snfge.org/resumes-2021/000650>

Invitation as a speaker

- « Le syndrome LPAC » at the XIIIe journée de FMC de la Somhad (Oran, Algeria, May 06, 2017)
- « Les maladies génétiques biliaires » at the XIIIe journée de FMC de la Somhad (Oran, Algeria, May 06, 2017)
- « EBM dans la maladie hémorroïdaire : traitement médical et instrumental » at the « Actualités d'octobre » of the SRBGE (Namur, Belgium, November 18, 2017)
- « Mécanismes physiopathologiques, conséquences nutritionnelles » at the session « Gastroparésie chronique » of the JFN (Journées Francophones de Nutrition), November 12, 2021 (virtual)

Training & transferable skills

- Course MD2290 "Science et médecine des animaux de laboratoire" (2017-2018, UCLouvain)
- Course MD2291 "Science et médecine des animaux de laboratoire" (2017-2018, UCLouvain)
- Training "CEBAM course" (2018, UCLouvain)
- Training "Pratique de la statistique avec R" (2019, UCLouvain)
- Training "Pratique de la statistique avec SAS" (2019, UCLouvain)

Curriculum vitæ

- Training "ImageJ « base »" (2019, URouen)
- Training "MacroJ" (2019, URouen)
- Training "Biostatistiques" (2019, URouen)
- Training "Spectrométrie de masse" (2019, URouen)
- Course "Pédagogie médicale" (2019-2020, URouen)
- Training "Analyses multivariées exploratoires en R" (2020, UCLouvain)
- Training "Initiation aux modèles d'équations structurelles (SEM) avec Stata" (2020, UCLouvain)

Other activities

Didactic work

- Writing for Menarini Benelux N.V./S.A.: « Syndrome de l'intestin irritable – quoi de neuf en 2020 ? Synthèse de la littérature et nouveautés de l'UEG Week Virtuelle 2020 » (2020)

Popular science

- Animation of the "Voyage dans le tube digestif" during the "Fête de la Science 2017" (2017, UFR Sciences, Normandy, France)

Faculty activities

- 2019-2021: Participation in the individual monitoring committee of one basic science PhD thesis committee as student representative of the doctoral student (Université de Rouen Normandie, France)
- 2022-: Member of the research laboratory and biobank committee, CHU UCL Namur



Suppléments – Addenda

Addendum 1. Supplementary data for Article 1**Supplementary Table 1.1.** *Grades of recommendation, assessment, development and evaluation approach*

Code	Quality of evidence	Definition
A	High quality	Further research is very unlikely to change the confidence in the estimate of effect
B	Moderate quality	Further research is likely to have an important impact on the confidence in the estimate of effect and may change the estimate
C	Low quality	Further research is very likely to have an important impact on the confidence in the estimate of effect and is like to change the estimate
D	Very low quality	Any estimated of effect is very uncertain

Adapted from Guyatt et al. (Guyatt et al., 2008).

Supplementary Table 1.2. *Details of extracted data among all articles included in the review.*

This Supplementary Table can be viewed on the cloud *via* the following link:

<https://www.dropbox.com/scl/fi/njowou9yxav6jezkicmmw/Supplementary-Table-1.2..docx?dl=0&rlkey=9u8oss9jyhxyshjx1iu24bhi1>



Addendum 2. Supplementary data for Article 2

Supplementary Table 2.1. Correlations between the global PSQI and different quantitative parameters in our population using Pearson correlation coefficient.

	R	95% CI	p-value
Age	0.21	0.11 to 0.30	< 0.0001
BMI	0.017	-0.087 to 0.12	0.017
Duration of FD symptoms	0.056	-0.048 to 0.16	0.29
GIQLI	-0.43	-0.51 to -0.34	< 0.0001
HADS	0.37	0.27 to 0.45	< 0.0001
HADS-A	0.28	0.18 to 0.38	< 0.0001
HADS-D	0.36	0.26 to 0.45	< 0.0001
ISI	-0.41	-0.50 to -0.32	< 0.0001
T½	0.20	-0.021 to 0.41	0.076
TSS	0.16	0.060 to 0.26	0.0021

BMI: body mass index, CI: confidence interval, FD: functional dyspepsia, GIQLI: GastroIntestinal Quality of Life Index, HADS: Hospital Anxiety and Depression Scale, HADS-A and HADS-D: HADS Anxiety and Depression subscales respectively, IBS: irritable bowel syndrome, PSQI: Pittsburgh Sleep Quality Index, TSS: Total Symptom Score, T½: gastric half-emptying time.

Supplementary Table 2.2. Comparison of FD patients with insomnia vs no insomnia

	No insomnia (n = 140)	Insomnia (n = 215)	p-value
Mean age, years ($\pm$ SD)	45.24 ($\pm$ 16.98)	47.92 ($\pm$ 14.74)	0.099
Mean BMI, kg.m⁻² ($\pm$ SD)	23.89 ($\pm$ 4.98)	24.27 ($\pm$ 5.28)	0.61
Sex ratio Male/Female (% women)	0.36 (73.57)	0.27 (78.60)	0.31
TSS, mean score ($\pm$ SD)	17.68 ($\pm$ 3.80)	19.19 ($\pm$ 3.54)	0.0002
Mean duration of FD symptoms, months ($\pm$ SD)	67.36 ($\pm$ 101.02)	81.87 ($\pm$ 98.76)	0.18
FD subtypes:			
<i>PDS, n (%)</i>	88 (62.86)	139 (64.65)	0.74
<i>EPS, n (%)</i>	20 (14.29)	21 (9.77)	0.23
<i>PDS+EPS, n (%)</i>	32 (22.86)	55 (25.58)	0.34
GIQLI, mean score ($\pm$ SD)	87.21 ($\pm$ 16.88)	72.62 ($\pm$ 18.20)	< 0.0001
GIQLI domains:			
<i>symptoms, mean score ($\pm$ SD)</i>	47.15 ($\pm$ 7.95)	42.61 ($\pm$ 8.83)	< 0.0001
<i>physical function, mean score ($\pm$ SD)</i>	14.44 ($\pm$ 5.50)	9.43 ($\pm$ 5.34)	< 0.0001
<i>emotional function, mean score ($\pm$ SD)</i>	11.33 ($\pm$ 4.09)	9.14 ($\pm$ 4.25)	< 0.0001
<i>social function, mean score ($\pm$ SD)</i>	10.91 ($\pm$ 3.71)	8.36 ($\pm$ 4.04)	< 0.0001
<i>treatment, mean score ($\pm$ SD)</i>	3.38 ($\pm$ 1.06)	3.07 ($\pm$ 1.24)	0.023
Smoking, n (%)	18 (12.86)	42 (19.53)	0.11
HADS, mean score ($\pm$ SD)	13.41 ($\pm$ 6.14)	18.66 ($\pm$ 7.14)	< 0.0001
HADS-A, mean subscale ($\pm$ SD)	8.40 ($\pm$ 3.77)	10.93 ($\pm$ 4.23)	< 0.0001

HADS-D, mean subscale ($\pm$ SD)	5.01 ($\pm$ 3.44)	7.73 ($\pm$ 4.10)	< 0.0001
Global PSQI, mean score ($\pm$ SD)	6.01 ($\pm$ 2.45)	10.82 ($\pm$ 3.31)	< 0.0001
Poor sleep quality (PSQI > 5), n (%)	98 (70.00)	214 (99.53)	< 0.0001
ISI, mean score ($\pm$ SD)	5.26 ($\pm$ 2.62)	15.89 ($\pm$ 4.16)	< 0.0001
Insomnia (ISI $\geq$ 10), n (%)	0 (0)	215 (100)	< 0.0001
IBS, n (%)	55 (39.29)	104 (48.37)	0.10
Heartburn, n (%)	33 (23.57)	63 (29.30)	0.27
Regurgitation, n (%)	58 (41.43)	99 (46.05)	0.44
Chest pain, n (%)	26 (18.57)	62 (28.84)	0.033
Any reflux symptom, n (%)	69 (49.29)	112 (52.09)	0.66
Gastric half-emptying time, minutes ($\pm$ SD)*	163.84 ($\pm$ 45.96)	164.92 ($\pm$ 69.59)	0.64
Delayed gastric emptying, n (%)*	17 (43.59)	14 (35.90)	0.64

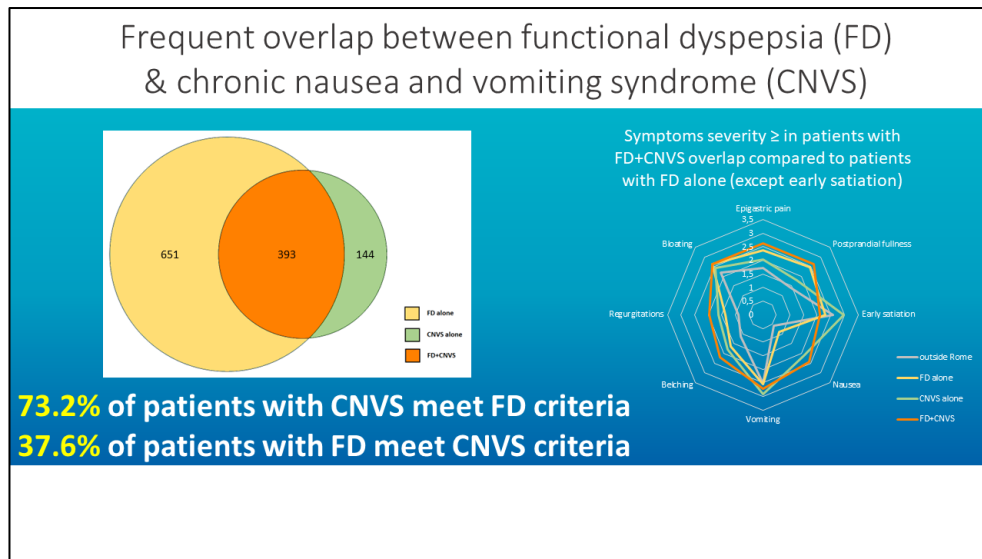
BMI: body mass index, EPS: epigastric pain syndrome, FD: functional dyspepsia, GIQLI: GastroIntestinal Quality of Life Index, HADS: Hospital Anxiety and Depression Scale, HADS-A and HADS-D: HADS Anxiety and Depression subscales respectively, IBS: irritable bowel syndrome, ISI: Insomnia Severity Index, n: number, PDS: postprandial distress syndrome, PSQI: Pittsburgh Sleep Quality Index, SD: standard deviation, TSS: Total Symptom Score.

* Only available for a subgroup of 78 (21.97%) patients.



Addendum 3. Supplementary data for Article 3

Graphical abstract



Supplementary Table 3.1. Comparison of patients with FD alone vs FD+CNVS overlap.

	FD alone (n = 651)	FD+CNVS (n = 393)	p-value
Mean age, years ($\pm$ SD)	46.8 ($\pm$ 15.4)	44.4 ($\pm$ 16.4)	0.011
Mean BMI, kg.m⁻² ($\pm$ SD)	24.6 ($\pm$ 5.2)	23.8 ($\pm$ 5.0)	0.026
PDS subgroup, n (%)	505 (77.6)	360 (91.6)	< 0.0001
Fibromyalgia, n (%)	45 (6.9)	26 (6.6)	0.85
Gender, sex ratio Male/Female (% females)	0.42 (70.4)	0.25 (80.2)	0.0005
GIQLI, mean score ($\pm$ SD)	82.5 ($\pm$ 19.4)	71.2 ($\pm$ 19.9)	< 0.0001
HADS-A, mean subscale ($\pm$ SD)	10.0 ($\pm$ 4.2)	10.3 ($\pm$ 4.3)	0.22
HADS-D, mean subscale ($\pm$ SD)	6.4 ($\pm$ 3.9)	7.0 ($\pm$ 4.2)	0.024
IBS overlap, n (%)	241 (37.0)	172 (43.8)	0.031
Migraine, n (%)	205 (31.5)	169 (43.0)	0.0002
PSQI, mean score ($\pm$ SD)	8.6 ($\pm$ 3.9)	9.7 ($\pm$ 3.8)	< 0.0001
BMI: body mass index, FD: functional dyspepsia, CNVS: chronic nausea and vomiting syndrome, GIQLI: GastroIntestinal Quality of Life Index, HADS: Hospital Anxiety and Depression Scale, HADS-A: HADS anxiety subscale, HADS-D: HADS depression subscale, IBS: irritable bowel syndrome, n: number, PDS: postprandial distress syndrome, PSQI: Pittsburgh Sleep Quality Index, SD: standard deviation.			

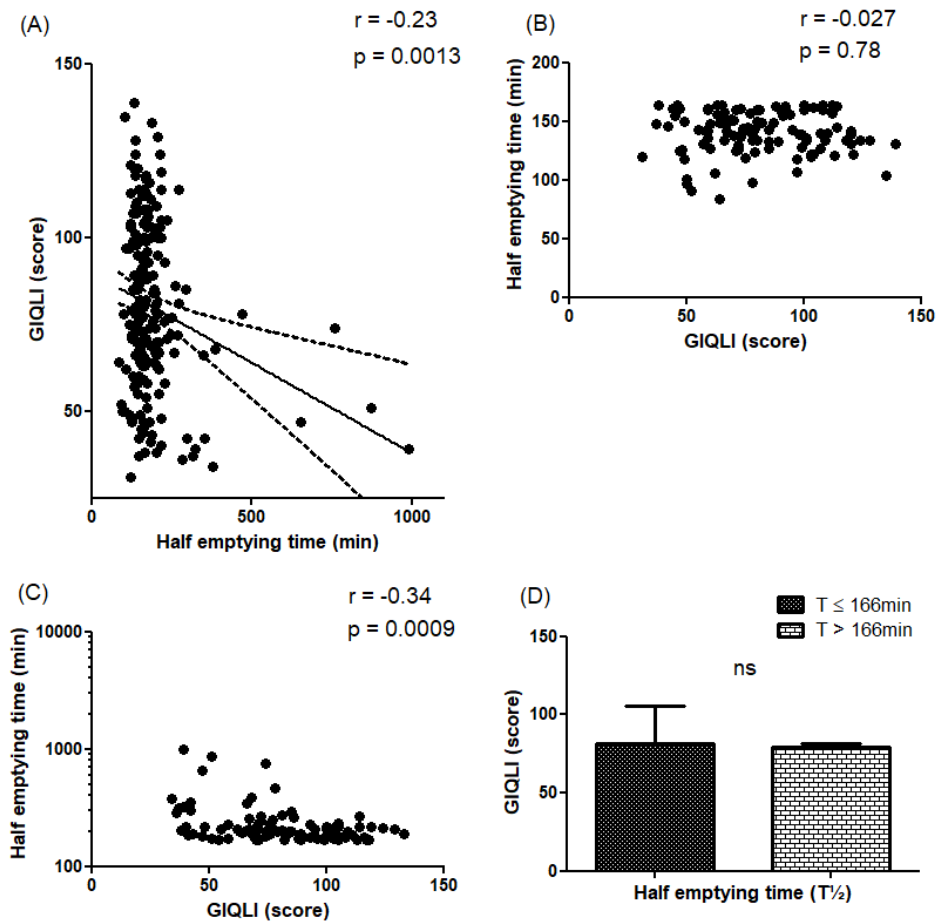
Supplementary Table 3.2. Multivariate logistic regression model of factors predicting CNVS overlap among all FD patients.

$R^2 = 0.105$.

	B	SE	OR	95% CI	p-value
Age	-0.012	0.004	0.99	0.98-1.00	0.008
Female gender	-0.32	0.16	0.73	0.53-1.00	0.050
GIQLI score	-0.031	0.004	0.97	0.96-0.98	< 0.0001
HADS-D subscale	-0.036	0.020	0.96	0.93-1.00	0.068
PDS subgroup	-0.91	0.21	0.40	0.27-0.61	< 0.0001
Constant	2.84	0.45	17.1		< 0.0001

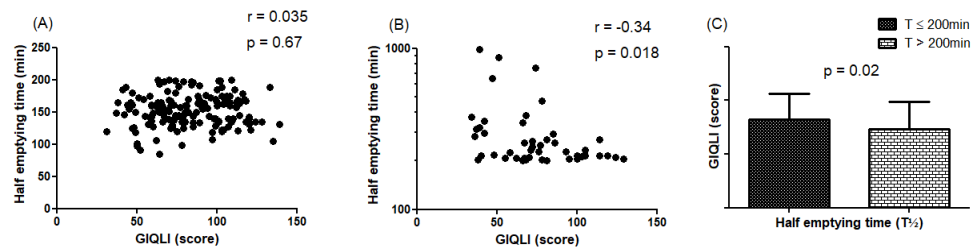
B: unstandardised regression coefficient, CI: confidence interval, FD: functional dyspepsia, CNVS: chronic nausea and vomiting syndrome, GIQLI: GastroIntestinal Quality of Life Index, HADS-D: Hospital Anxiety and Depression Scale - Depression subscale, OR: odds ratio, PDS: postprandial distress syndrome, SE: standard error. Factors independently associated with overlapping CNVS among FD patients are indicated in bold.

Addendum 4. Supplementary data for Article 4



Supplementary Figure 4.1. Analyses of the GIQLI score.

Linear regression analysis with the regression line best predicting the Gastrointestinal Quality of Life Index (GIQLI score) from gastric half-emptying time ($T_{1/2}$) calculated over 6-8 hours for the overall patient population (A), correlation among patients with $T_{1/2} \leq 166$ min (B), correlation among patients with $T_{1/2} > 166$ min (C) and the mean GIQLI score between $T_{1/2} \leq 166$ min and >166 min (D).
 ns: non-significant.



Supplementary Figure 4.2. Correlation of the GastroIntestinal Quality of Life Index (GIQLI score) among patients with gastric half-emptying time ($T_{1/2} \leq 200$ min (A), $T_{1/2} > 200$ min (B) and comparison of the mean GIQLI score between patients with a $T_{1/2} \leq 200$ min vs > 200 min (C) (calculated over 6-8 hours).

Supplementary Table 4.1. Characteristics of patients with functional dyspepsia.

	Patients (n = 105)
Mean age, years (range)	47.8 (18-82)
Mean BMI, kg.m⁻² (± SD)	23.3 (± 5.5)
Sex ratio Male/Female (% males)	0.48 (32.4)
Mean T½ over 6-8 hours, min (± SD)	172.0 (± 72.9)
Mean T½ calculated over 4 hours, min (± SD)	160.8 (± 61.5)
Surgery for GORD or HH, n (%)	15 (14.3)
FD subtypes:	
PDS, n (%)	88 (83.8)
EPS, n (%)	21 (20.0)
PDS+EPS, n (%)	13 (12.4)
Overlap with IBS, n (%)	34 (32.4)
Episode of gastroenteritis before the onset of symptoms, n (%)	5 (4.8)
TSS, mean score (± SD)	15.8 (± 5.8)
GIQLI, mean score (± SD)	77.4 (± 22.7)
HADS, mean score (± SD)	15.8 (± 7.3)
HADS-A, mean subscore (± SD)	9.4 (± 4.2)
HADS-D, mean subscore (± SD)	6.4 (± 4.3)
BMI: body mass index, EPS: epigastric pain syndrome, FD: functional dyspepsia, GORD: gastro-oesophageal reflux disease, GIQLI: GastroIntestinal Quality of Life Index, HADS: Hospital Anxiety and Depression Scale, HADS-A and HADS-D: HADS Anxiety and Depression subscales respectively, HH: hiatal hernia, IBS: irritable bowel syndrome, n = number, PDS: postprandial distress syndrome, SD: standard deviation, T½: gastric half-emptying time, TSS: Total Symptom Score.	

Supplementary Table 4.2. Characteristics of the population according to gastric half-emptying time ($T_{1/2}$) ≤ 166 min or > 166 min (measured over 6-8 hours) in functional dyspepsia (FD) patients.

	$T_{1/2} \leq 166$ min (n = 60)	$T_{1/2} > 166$ min (n = 45)	p-value
Mean age, years ($\pm$ SD)	46.3 ($\pm$ 16.3)	49.8 ($\pm$ 14.7)	0.27
Mean BMI, kg.m⁻² ($\pm$ SD)	21.9 ($\pm$ 5.0)	25.1 ($\pm$ 5.5)	0.0029*
Sex ratio Male/Female (% males)	0.43 (30.0)	0.55 (35.6)	0.67
FD subtypes:			
PDS, n (%)	51 (85.0)	37 (82.2)	0.79
EPS, n (%)	12 (20.0)	9 (20.0)	1.00
PDS+EPS, n (%)	8 (13.3)	5 (11.1)	/
Surgery for GORD or HH, n (%)	9 (15.0)	6 (13.3)	1.00
Overlap with IBS, n (%)	23 (38.3)	11 (24.4)	0.15
Episode of gastroenteritis before the onset of symptoms, n (%)	2 (3.3)	3 (6.7)	0.65
TSS, mean score ($\pm$ SD)	15.6 ($\pm$ 5.4)	16.2 ($\pm$ 6.2)	0.64
GIQLI, mean score ($\pm$ SD)	75.6 ($\pm$ 23.1)	79.8 ($\pm$ 22.0)	0.35
HADS, mean score ($\pm$ SD)	15.6 ($\pm$ 6.8)	16.1 ($\pm$ 8.0)	0.72
HADS-A, mean subscore ($\pm$ SD)	9.2 ($\pm$ 3.8)	9.7 ($\pm$ 4.6)	0.59
HADS-D, mean subscore ($\pm$ SD)	6.4 ($\pm$ 4.3)	6.4 ($\pm$ 4.3)	0.93
BMI: body mass index, EPS: epigastric pain syndrome, HH: hiatal hernia, GORD: gastro-oesophageal reflux disease, GIQLI: GastroIntestinal Quality of Life Index, HADS: Hospital Anxiety and Depression Scale, HADS-A and HADS-D: HADS Anxiety and Depression subscales respectively, IBS: irritable bowel syndrome, n = number, PDS: postprandial distress syndrome, SD: standard deviation, TSS: Total Symptom Score. * p < 0.05			

Supplementary Table 4.3. Symptoms according to gastric half-emptying time ($T_{1/2}$) ≤ 166 min or > 166 min (measured over 6-8 hours) in functional dyspepsia patients.

	$T_{1/2} \leq 166$ min (n = 60)	$T_{1/2} > 166$ min (n = 45)	p-value
<i>Postprandial fullness, n (mean score)</i>	35 (1.3)	26 (1.3)	1.00
<i>Abdominal pain, n (mean score)</i>	29 (1.5)	21 (1.8)	1.00
<i>Bloating, n (mean score)</i>	31 (1.6)	26 (1.4)	0.56
<i>Regurgitations, n (mean score)</i>	18 (2.3)	15 (2.3)	0.83
<i>Nausea, n (mean score)</i>	19 (2.2)	16 (2.3)	0.68
<i>Early satiety, n (mean score)</i>	33 (1.6)	20 (1.8)	0.33
<i>Belching, n (mean score)</i>	30 (1.7)	18 (2.0)	0.33
<i>Vomiting, n (mean score)</i>	4 (3.4)	4 (3.4)	0.72
<i>TSS, mean score ($\pm$ SD)</i>	15.6 ($\pm$ 5.4)	16.2 ($\pm$ 6.2)	0.64
n = number, TSS: Total Symptom Score.			

Supplementary Table 4.4. Univariate analysis of factors predicting gastric half-emptying time ($T_{1/2}$) ≤ 200 min or > 200 min (calculated over 8 hours).

Parameter	p-value
Age	0.78
BMI	0.76
Diabetes mellitus	0.005
Gender	0.65
GIQLI	0.042
Heartburn	0.86
IBS	0.77
BMI: body mass index, GIQLI: GastroIntestinal Quality of Life Index, IBS: irritable bowel syndrome.	

Supplementary Table 4.5. Multivariate analysis of factors predicting gastric half-emptying time ($T_{1/2}$) ≤ 200 min or > 200 min (calculated over 8 hours).

Parameter	p-value
<i>Age</i>	0.79
<i>BMI</i>	0.80
<i>Diabetes mellitus</i>	0.007
<i>Gender</i>	0.68
<i>GIQLI</i>	0.044
<i>Heartburn</i>	0.83
<i>IBS</i>	0.69
BMI: body mass index, GIQLI: GastroIntestinal Quality of Life Index, IBS: irritable bowel syndrome.	

Supplementary Table 4.6. Characteristics of the population according to gastric half-emptying time ($T_{1/2} \leq 200$ min or > 200 min (measured over 6-8 hours) in functional dyspepsia (FD) patients.

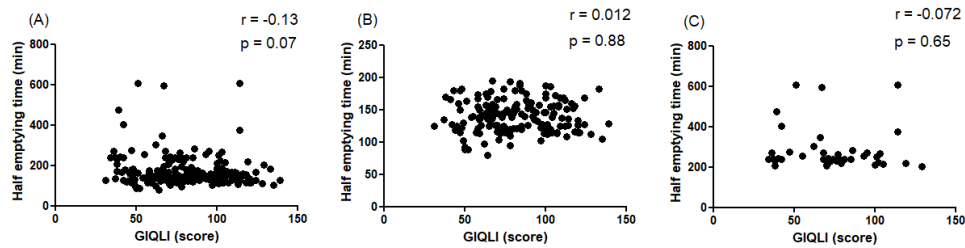
	$T_{1/2} \leq 200$ min (n = 85)	$T_{1/2} > 200$ min (n = 20)	p-value
Mean age, years ($\pm$ SD)	46.6 ($\pm$ 16.1)	52.8 ($\pm$ 13.1)	0.12
Mean BMI, kg.m⁻² ($\pm$ SD)	23.1 ($\pm$ 5.7)	24.2 ($\pm$ 4.1)	0.40
Sex ratio Male/Female (% males)	0.49 (32.9)	0.43 (30.0)	1.00
FD subtypes:			
PDS, n (%)	69 (81.2)	19 (30.0)	0.18
EPS, n (%)	17 (20.0)	4 (20.0)	1.00
PDS+EPS, n (%)	9 (10.6)	4 (20.0)	0.27
Surgery for GORD or HH, n (%)	11 (12.9)	4 (20.0)	0.48
Overlap with IBS, n (%)	29 (32.9)	5 (25.0)	0.60
Episode of gastroenteritis before the onset of symptoms, n (%)	3 (3.5)	2 (10.0)	0.24
TSS, mean score ($\pm$ SD)	16.3 ($\pm$ 5.8)	13.8 ($\pm$ 5.1)	0.072
GIQLI, mean score ($\pm$ SD)	78.0 ($\pm$ 23.2)	74.6 ($\pm$ 20.3)	0.55
HADS, mean score ($\pm$ SD)	15.6 ($\pm$ 6.8)	16.6 ($\pm$ 9.2)	0.60
HADS-A, mean subscore ($\pm$ SD)	9.3 ($\pm$ 3.8)	9.9 ($\pm$ 5.5)	0.56
HADS-D, mean subscore ($\pm$ SD)	6.3 ($\pm$ 4.3)	6.7 ($\pm$ 4.2)	0.73
BMI: body mass index, HH: hiatal hernia, GORD: gastro-oesophageal reflux disease, GIQLI: GastroIntestinal Quality of Life Index, HADS: Hospital Anxiety and Depression Scale, HADS-A and HADS-D: HADS Anxiety and Depression subscales respectively, IBS: irritable bowel syndrome, n = number, SD: standard deviation, TSS: Total Symptom Score.			

Supplementary Table 4.7. Symptoms according to gastric half-emptying time ($T_{1/2}$) ≤ 200 min or > 200 min (measured over 6-8 hours) in functional dyspepsia patients.

	$T_{1/2} \leq 200$ min (n = 85)	$T_{1/2} > 200$ min (n = 20)	p-value
<i>Postprandial fullness, n (mean score)</i>	46 (1.4)	15 (1.0)	0.13
<i>Abdominal pain, n (mean score)</i>	38 (1.7)	12 (1.4)	0.32
<i>Bloating, n (mean score)</i>	42 (1.6)	15 (1.1)	0.048*
<i>Regurgitations, n (mean score)</i>	28 (2.3)	5 (2.4)	0.60
<i>Nausea, n (mean score)</i>	26 (2.3)	9 (1.8)	0.29
<i>Early satiety, n (mean score)</i>	41 (1.7)	12 (1.4)	0.46
<i>Belching, n (mean score)</i>	39 (1.9)	9 (1.6)	1.00
<i>Vomiting, n (mean score)</i>	6 (3.4)	2 (3.3)	0.65
<i>TSS, mean score ($\pm$ SD)</i>	16.3 ($\pm$ 5.8)	13.8 ($\pm$ 5.1)	0.072
n = number, TSS: Total Symptom Score. * p < 0.05			

Supplementary Table 4.8. Symptoms according to gastric half-emptying time ($T_{1/2}$) ≤ 200 min or > 200 min (calculated over 4 hours).

	$T_{1/2} \leq 200$ min (n = 157)	$T_{1/2} > 200$ min (n = 41)	p-value
Postprandial fullness, n (mean score)	75 (1.7)	27 (1.1)	0.053
Abdominal pain, n (mean score)	55 (2.0)	22 (1.7)	0.033*
Bloating, n (mean score)	73 (1.7)	26 (1.3)	0.079
Regurgitations, n (mean score)	51 (2.3)	13 (2.2)	1.00
Nausea, n (mean score)	40 (2.4)	14 (2.2)	0.32
Early satiety, n (mean score)	61 (2.1)	22 (1.7)	0.11
Belching, n (mean score)	64 (2.0)	20 (1.6)	0.38
Vomiting, n (mean score)	16 (3.4)	3 (3.1)	0.77
TSS, mean score ($\pm$ SD)	16.8 ($\pm$ 6.1)	14.3 ($\pm$ 5.8)	0.024*
n = number, TSS: Total Symptom Score. * p < 0.05			



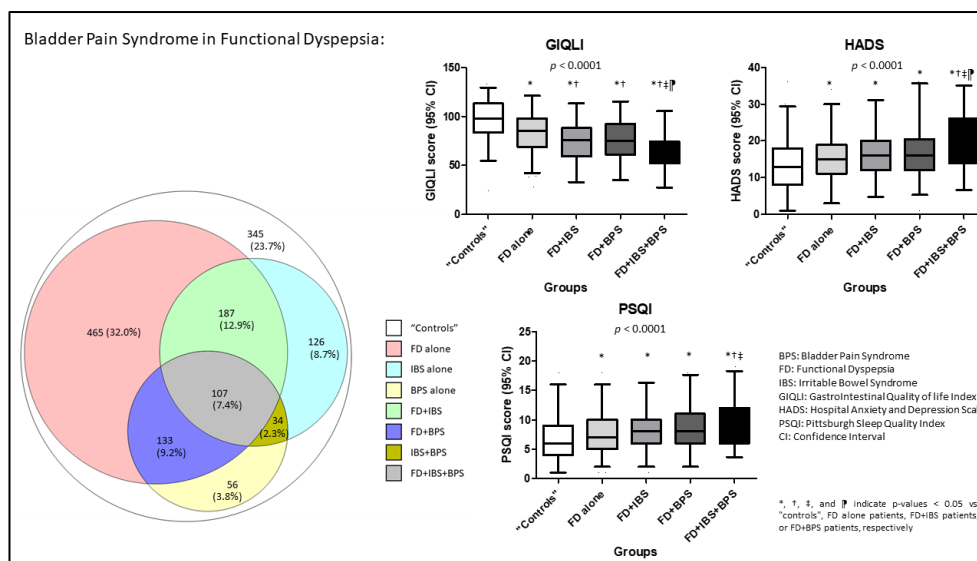
Supplementary Figure 4.3. Correlation between the GIQLI score and gastric half-emptying time.

Correlation between the GastroIntestinal Quality of Life Index (GIQLI score) and the gastric half-emptying time ($T_{1/2}$) calculated over four hours for the entire population (A), for patients with a $T_{1/2} \leq 200$ min (B), and those with a $T_{1/2} > 200$ min (C).

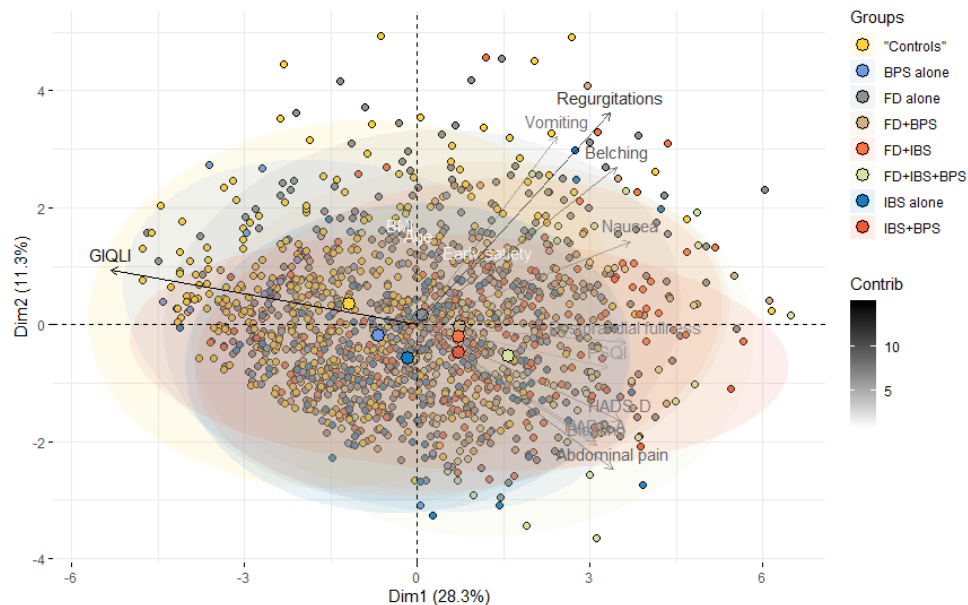


Addendum 5. Supplementary data for Article 5

Graphical abstract

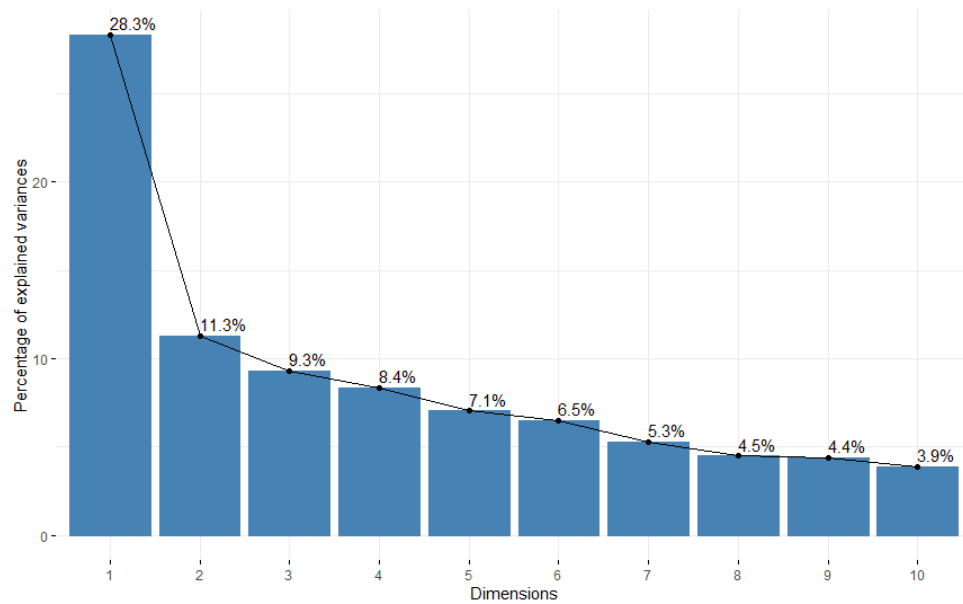


Bladder pain syndrome is present in 26.9% of functional dyspepsia patients and is associated with higher gastrointestinal, psychological distresses and sleep symptom burdens, and with reduced quality of life. We recommend to systematically assess the presence of bladder pain syndrome in patients with functional dyspepsia.



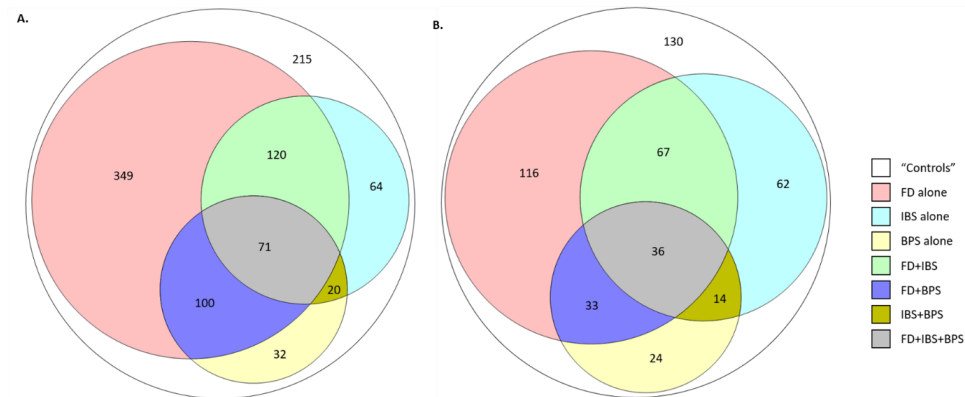
Supplementary Figure 5.1. Principal Component Analysis (PCA) biplot of the overall dataset.

Factors used were age, body mass index (BMI), GastroIntestinal Quality of Life Index (GIQLI), Hospital Anxiety and Depression Scale (HADS) subscales, Pittsburgh Sleep Quality Index (PSQI), and eight dyspeptic symptoms (postprandial fullness, abdominal pain, bloating, regurgitations, nausea, early satiety, belching and vomiting). We used all dimensions with eigenvalues superior to one to select principal components for analysis. Visual analysis does not enable to differentiate groups due to broad overlap between diagnostic groups. The GIQLI behaves independently from other scores (HADS-A and HADS-D subscales, and PSQI). The contribution of the different variables to the two principal components (PC1 and PC2) is represented using a grey scale. 95% confidence intervals are represented by ellipses. "Controls" stands for "symptomatic controls" in the legend on x axis. BPS: bladder pain syndrome, FD: functional dyspepsia, IBS: irritable bowel syndrome.



Supplementary Figure 5.2. Principal Component Analysis (PCA) scree plot of the overall dataset.

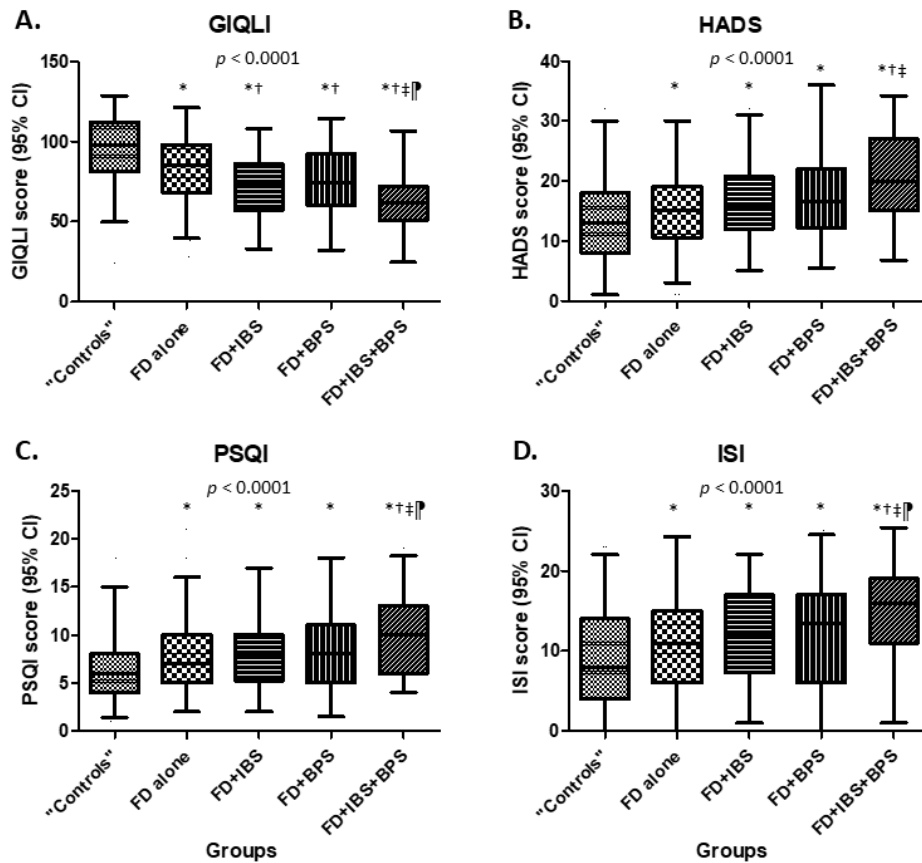
The first four dimensions have an eigenvalue superior to one and explain more than 57.26% of the total variance.



Supplementary Figure 5.3. Venn diagram summarising overlap syndromes in the Rome III (A) and Rome IV (B) cohorts.

The numbers of subjects within each diagnostic group are shown, with areas of the circles being proportionate to the number of patients. The Rome III population comprises 640 patients with FD, 275 patients with IBS and 223 patients with BPS among a total of 971 subjects. The Rome IV population comprises 252 patients with FD, 179 patients with IBS and 107 patients with BPS among a total of 482 subjects. "Controls" stands for "symptomatic controls" in the legend.

BPS: bladder pain syndrome, FD: functional dyspepsia, IBS: irritable bowel syndrome.

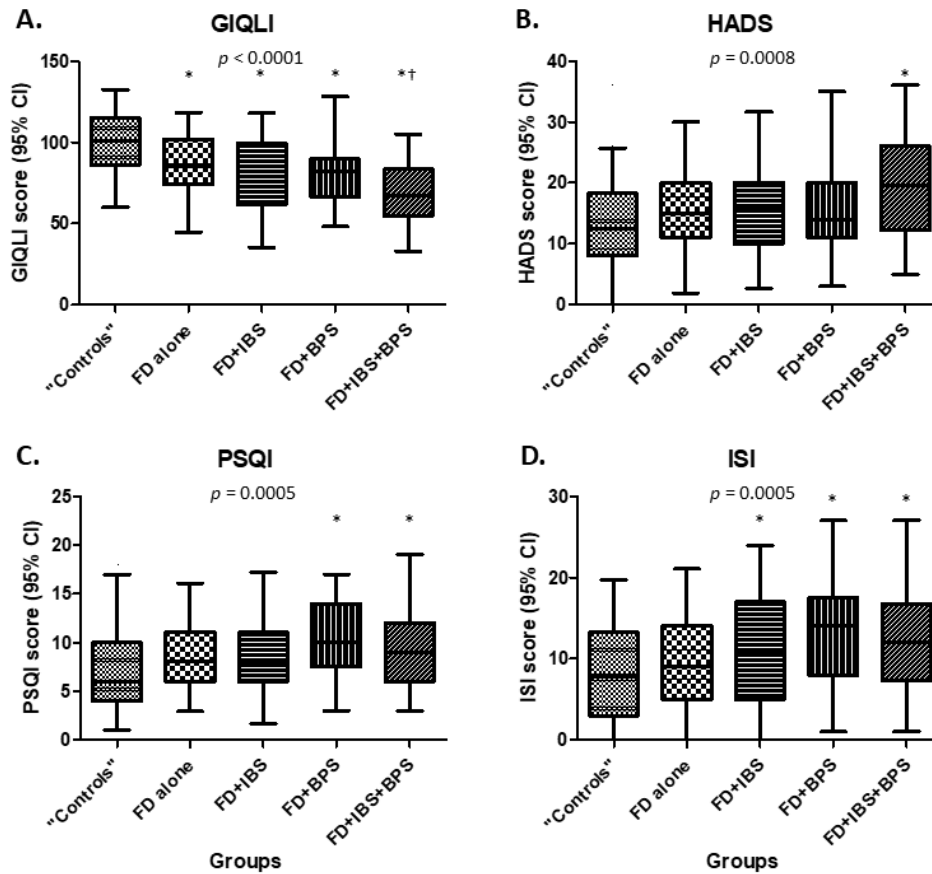


Supplementary Figure 5.4. Different characteristics of the Rome III population according to the group.

Comparisons of (A) GastroIntestinal Quality of Life Index (GIQLI), (B) Hospital Anxiety and Depression Scale (HADS), (C) Pittsburgh Sleep Quality Index (PSQI), and (D) Insomnia Severity Index (ISI) between the 5 different diagnostic groups (Controls, FD without overlap (FD alone), FD with IBS (FD+IBS), FD with BPS (FD+BPS) and FD with both IBS and BPS (FD+IBS+BPS)) in the Rome III cohort.

Results are presented as whiskers with 95% confidence interval (CI). The symbols *, †, ‡ and ¶ indicate p-values < 0.05 vs controls, FD alone patients, FD+IBS patients, or FD+BPS patients respectively. "Controls" stands for "symptomatic controls" in the legend on x axis.

BPS: bladder pain syndrome, FD: functional dyspepsia, IBS: irritable bowel syndrome.



Supplementary Figure 5.5. Different characteristics of the Rome IV population according to the group.

Comparisons of (A) GastroIntestinal Quality of Life Index (GIQLI), (B) Hospital Anxiety and Depression Scale (HADS), (C) Pittsburgh Sleep Quality Index (PSQI), and (D) Insomnia Severity Index (ISI) between the 5 different diagnostic groups (Controls, FD without overlap (FD alone), FD with IBS (FD+IBS), FD with BPS (FD+BPS) and FD with both IBS and BPS (FD+IBS+BPS)) in the Rome IV cohort.

Results are presented as whiskers with 95% confidence interval (CI). The symbols * and † indicate p -values < 0.05 vs controls or FD alone patients respectively. "Controls" stands for "symptomatic controls" in the legend on x axis.

BPS: bladder pain syndrome, FD: functional dyspepsia, IBS: irritable bowel syndrome.

Supplementary Table 5.1. 8-item symptom-based self-questionnaire based on the ESSIC criteria published in 2008 for the diagnosis of bladder pain syndrome.

Item	Question
1.	Do you have pain that gets worse as your bladder fills?
2.	Do you have any discomfort that gets worse as your bladder fills?
3.	Do you have a feeling of heaviness which is even more important as your bladder fills?
4.	Have the symptoms lasted for more than 6 months?
5.	Do you suffer from the urge to urinate urgently?
6.	Do you suffer from the urge to urinate permanently?
7.	Do you urinate more than 8 times during daytime?
8.	Do you urinate more than once a night?

Supplementary Table 5.2. Main data of each active variable used in the Principal Component Analysis (PCA).

Variables	Coordinates	Contributions	Cos2
GIQLI	-0.90	20.3	0.80
Nausea	0.62	9.79	0.39
Postprandial fullness	0.61	9.33	0.37
HADS-D	0.59	8.86	0.35
Belching	0.58	8.58	0.34
Abdominal pain	0.57	8.24	0.33
Regurgitations	0.56	8.04	0.32
PSQI	0.56	7.85	0.31
Bloating	0.52	6.93	0.28
HADS-A	0.52	6.81	0.27
Vomiting	0.41	4.18	0.17
Early satiety	0.21	1.08	0.043
BMI	-0.05	0.06	0.002
Age	0.005	0.00	0.00
BMI: body mass index, GIQLI: GastroIntestinal Quality of Life Index, HADS: Hospital Anxiety and Depression Scale, HADS-A and HADS-D: HADS Anxiety and Depression subscales respectively, PSQI: Pittsburgh Sleep Quality Index.			

Supplementary Table 5.3. Multivariate linear regression model with BPS as the dependent variable.

$R^2 = 0.06$.

	B	Standard Error	β	p-value
Constant	0.41	0.13		
Age	-0.001	0.001	-0.019	0.56
BMI	-0.003	0.003	-0.037	0.26
Gender	0.028	0.035	0.027	0.42
GIQLI	-0.003	0.001	-0.13	0.001
HADS	0.003	0.001	0.068	0.062
IBS	0.097	0.032	0.10	0.003
PSQI	0.005	0.004	0.044	0.24
BMI: body mass index, GIQLI: GastroIntestinal Quality of Life Index, HADS: Hospital Anxiety and Depression Scale, IBS: irritable bowel syndrome, PSQI: Pittsburgh Sleep Quality Index. Factors independently associated with overlap with BPS in FD patients are indicated in bold.				



Addendum 6. Supplementary data for Article 6

Supplementary Table 6.1. Primer sequences for the targeted mouse genes for polymerase chain reaction.

Gene	Sequences	Annealing Temperature (°C)
<i>TNF-α</i>	Sense: 5'-TGTCTACTCCTCAGAGCCCC-3' Antisense: 5'-TGAGTCCTTGATGGTGGTGC-3'	60
<i>IL-18</i>	Sense: 5'-CCCAAAAGATGAAGGGCTGC-3' Antisense: 5'-AAGGTCCACGGGAAAGACAC-3'	59
<i>IL-10</i>	Sense: 5'-ACCTGGTAGAAGTGATGCCC-3' Antisense: 5'-GCTCCACTGCCTTGCTCTTAT-3'	59
IL: Interleukin, TNF: Tumour necrosis factor.		



Addendum 7. Supplementary data for Article 7

Supplementary table 7.1. Characteristics of animals from the first series according to the three groups (saline, TNBS at day 2 and TNBS at day 7).

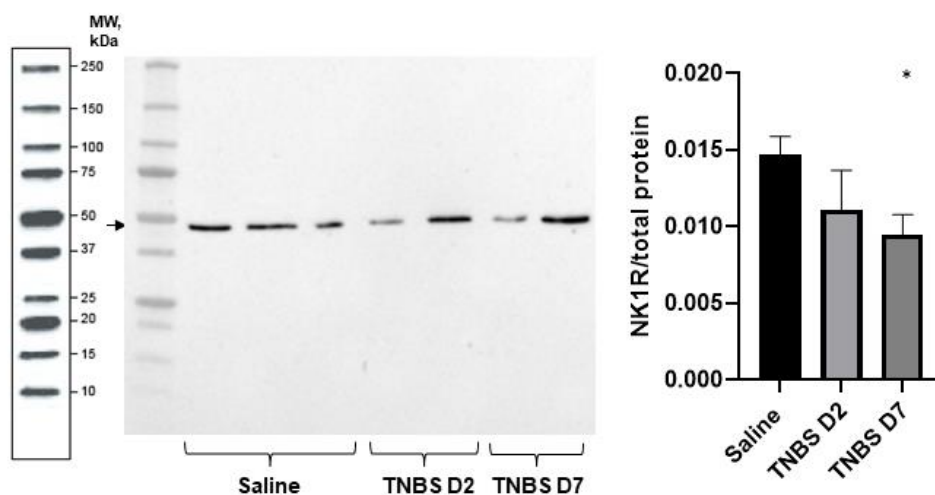
	Saline (n = 12)	TNBS D2 (n = 9)	TNBS D7 (n = 15)	p-value
Age (day of experiment), d ($\pm$ SEM)	54.5 ($\pm$ 0.5)	53.0 ($\pm$ 0.6)	54.0 ($\pm$ 0.5)	0.19
Weight (day of experiment), g ($\pm$ SEM)	344.9 ($\pm$ 6.1)	328.2 ($\pm$ 8.1)	338.1 ($\pm$ 6.2)	0.34
Weight (day of distensions), g ($\pm$ SEM)	367.8 ($\pm$ 6.0)	311.2 ($\pm$ 7.8)	356.2 ($\pm$ 6.1)	0.0002*
Faecal pellet output H+1, n ($\pm$ SEM)	1.7 ($\pm$ 0.5)	1.4 ($\pm$ 0.6)	3.0 ($\pm$ 0.6)	0.14
Stool consistency at D1, % water ($\pm$ SEM)	65.6 ($\pm$ 1.6)	64.7 ($\pm$ 0.0) [†]	74.9 ($\pm$ 1.9)	0.0047**
Macroscopic score, mean score ($\pm$ SEM)	0.0 ($\pm$ 0.0)	1.3 ($\pm$ 0.3)	1.1 ($\pm$ 0.3)	0.0003*, **
Gastric weight, g ($\pm$ SEM)	2.2 ($\pm$ 0.06)	2.0 ($\pm$ 0.1)	2.3 ($\pm$ 0.08)	0.31
Colonic weight, g ($\pm$ SEM)	2.0 ($\pm$ 0.09)	2.4 ($\pm$ 0.1)	2.3 ($\pm$ 0.08)	0.011*, **
Colonic length, cm ($\pm$ SEM)	24.9 ($\pm$ 0.6)	23.0 ($\pm$ 0.8)	23.3 ($\pm$ 0.7)	0.10
Weight-length ratio, mg/cm ($\pm$ SEM)	80.1 ($\pm$ 3.5)	107.3 ($\pm$ 8.0)	98.9 ($\pm$ 5.3)	0.0076*, **
Phenobarbital use, mL/g ($\pm$ SEM)	0.3 ($\pm$ 0.01)	0.3 ($\pm$ 0.01)	0.3 ($\pm$ 0.01)	0.13

Suppléments

d: days, D1: day 1, D2: day 2, D7: day 7, g: grams, H+1: one hour after intracolonic administration, n: number, SEM: standard error of the mean, TNBS: 2,4,6-trinitrobenzene sulphonic acid.

The symbols * and ** indicate p-values < 0.05 in TNBS D2 vs saline and TNBS D7 vs saline groups respectively, whereas mentioned p-values concern the results of the Kruskal-Wallis test (one-way ANOVA) analysing all groups together.

[†] only available for 1 rat.



Supplementary figure 7.1. Expression of NK1R.

Expression of neurokinin 1 receptor (NK1R) at the T8-T9 level of the spinal cord, with quantitative analysis (ratio to total proteins) on the right, in rats with intracolonic administration of saline (NaCl 0.9%) at day 7 or TNBS (25mg) on day 2 (D2) and day 7 (D7). Protein ladder for MW determination is shown on the left; the arrow corresponds to the MW of NK1R (46 kDa). N = 8-14 rats per group. Variability in the results is represented by the mean and the standard error of the mean.

* $p < 0.05$ (compared to the saline group)

MW: molecular weight, TNBS: 2,4,6-trinitrobenzene sulphonic acid.



Addendum 8. Other works associated with the thesis

Letter to the editor (E-letter) in the Journal of Clinical Investigation 2018

Title

Akkermansia muciniphila in functional GI disorders: good rather than evil?

Authors

Fabien Wuestenberghs, Guillaume Gourcerol, Pierre Déchelotte, and Moïse Coëffier

Affiliation

Normandie Univ, UNIROUEN, INSERM UMR 1073, Nutrition, Gut & Brain Laboratory, Institute for Biomedical Research and Innovation (IRIB) and Rouen University Hospital, Nutrition and Physiology Departments, Rouen, France

Dear editor,

We have read with interest the research paper of Zhou et al. concerning the impact of FODMAPs on visceral nociception. Interestingly, authors reported that *Akkermansia muciniphila* was increased by 4.7-fold among Gram-negative bacteria following a high-FODMAP diet. This mucin-degrading bacterium is usually considered beneficial for gut epithelium and in metabolic syndrome. However, its role in irritable bowel syndrome (IBS) seems ambiguous. Indeed, Zhou et al. have shown that rats developed micro-inflammation, increased gut permeability and visceral hypersensitivity following a high-FODMAP diet. These alterations were driven by diet-induced change in microbiota. Since *A. muciniphila* shows the highest relative change in their model, authors speculate that the bacterium plays a key role in the pathophysiology. Clinically, even if we can accept that increased *A. muciniphila* in the microbiota of pediatric IBS patients seems to be correlated with digestive complaints (1), it is less clear in adults since the correlation coefficient was only 0.27 in the study of Rajilic et al. (2). Other studies in the literature rather suggest a beneficial effect of *A. muciniphila* on intestinal barrier: *in vitro* studies suggest that *A. muciniphila* strengthens the integrity of epithelial

cell layer in the gut (3). Finally, the bacterium exhibited a preventive effect on DSS-induced colitis (4) and its extracellular vesicles enhanced tight junction function (5).

In conclusion, the implication of *A. muciniphila* with gut health is more complex than suggested by Zhou et al. and requires further studies. The observed increase in *A. muciniphila* relative abundance after high FODMAPs may be just an adaptative process tending to reduce inflammation rather than a contributor to hypersensitivity. Further studies are needed, including quantitative microbiome profiling approaches as well as molecular/mechanistic studies to substantiate the role of *A. muciniphila* in IBS.

Kind regards.

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- (1) Saulnier DM, et al. Gastrointestinal microbiome signatures of pediatric patients with irritable bowel syndrome. *Gastroenterology* 2011;141(5):1782-1791.
- (2) Rajilic-Stojanovic M, et al. Global and deep molecular analysis of microbiota signatures in fecal samples from patients with irritable bowel syndrome. *Gastroenterology* 2011;141(5):1792-1801.
- (3) Reunanen J, et al. *Akkermansia muciniphila* adheres to enterocytes and strengthens the integrity of the epithelial cell layer. *Appl Environ Microbiol.* 2015;81(11):3655-3662.
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- (5) Chelakkot C, et al. *Akkermansia muciniphila*-derived extracellular vesicles influence gut permeability through the regulation of tight junctions. *Exp Mol Med.* 2018;50(2):e450.

Fabien Wuestenberghs, Guillaume Gourcerol, Pierre Déchelotte, Moïse Coëffier. *Akkermansia muciniphila* in functional GI disorders: good rather than evil? *The Journal of Clinical Investigation* 2018 (E-letter)

Link: <https://www.jci.org/eletters/view/92390#sec1>

NeuroGASTRO 2019 Abstract #265

Title

Irritable Bowel Syndrome And Bladder Pain Syndrome Comorbidities Are Associated With Altered Quality Of Life, Anxiety, Depression And Sleep In Patients With Functional Dyspepsia

Authors

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Background/Aims

Functional dyspepsia (FD) and irritable bowel syndrome (IBS) are known to overlap. However, the impact of overlap between bladder pain syndrome (BPS) and FD remains unknown. Our aim was to evaluate the presence and the impact of IBS and/or BPS in FD patients.

Methods

1,598 consecutive patients with investigated dyspeptic symptoms were studied. Functional dyspepsia and IBS were diagnosed according to Rome criteria. Presence of BPS was assessed using NIDDK 2006 criteria. Quality of life was quantified by the GastroIntestinal Quality of Life Index (GIQLI). Anxiety and depression were evaluated using the Hospital Anxiety and Depression (HAD) scale.

Suppléments

Sleep was assessed using the Pittsburgh Sleep Quality Index (PSQI) and the Insomnia Severity Index (ISI).

Key results

Among all dyspeptic patients, 892 patients fit Rome criteria for FD. 476 fit only criteria for FD (FD-only), 200 fit both FD and IBS criteria (FD+IBS) and 122 fit both FD and BPS criteria (FD+BPS). 94 fit all criteria for FD, IBS and BPS (FD+IBS+BPS). 430 patients were free of diagnostic criteria for FD, IBS and BPS and served as a control group. Age differed among the groups ($p = 0.0002$), patients with IBS being younger. Female predominance increased with increasing comorbidities ($p < 0.0001$). QIGLI score in the control group was 95.6 and was decreased in FD-only patients (84.1; $p < 0.0001$), in FD+IBS (74.4; $p < 0.0001$) and FD+BPS patients (75.5; $p < 0.0001$) compared to FD-only patients and was further decreased in patients with FD+IBS+BPS patients (63.7; $p < 0.0001$) (Figure 1). The HAD scale increased with the number of diagnostics (13.6 in the control group; 15.2 in FD-only patients; 16.5 and 16.9 in FD+IBS and FD+BPS patients respectively; 19.7 in FD+IBS+BPS patients; $p < 0.0001$). The PSQI and ISI scores also increased with the number of diagnostics, with the poorest quality of sleep observed in patients with FD+IBS+BPS.

Conclusions

Overlaps between FD and IBS and/or BPS are frequent, since IBS was present in 33% and BPS in 24% of FD patients respectively. Associated diagnosis of IBS and BPS decreased quality of life, altered anxiety-depression scale and were associated with altered sleep in patients with FD.

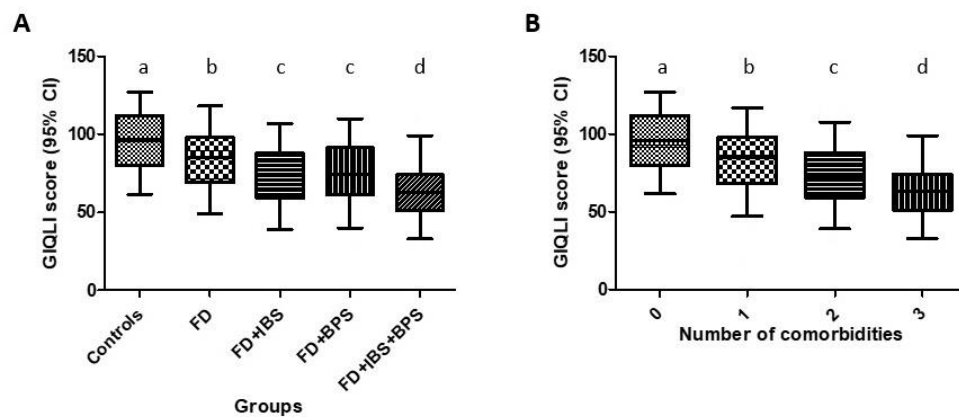


Figure 1. Comparisons of the mean GIQLI score (whiskers with 95% CI) between different diagnostic groups (A) and between groups of increasing number of comorbidities (none, FD, IBS and BPS) (B). Groups without common letters significantly differ ($p < 0.0001$).

BPS: bladder pain syndrome, CI: confidence interval, FD: functional dyspepsia, GIQLI: GastroIntestinal Quality of Life Index, IBS: irritable bowel syndrome.

Fabien Wuestenberghs, Maximilien Baron, Chloé Melchior, Charlotte Desprez, Jean-Nicolas Cornu, Anne-Marie Leroi, Guillaume Gourcerol. Irritable bowel syndrome and bladder pain syndrome comorbidities are associated with altered quality of life, anxiety, depression and sleep in patients with functional dyspepsia [abstract 265]. *Neurogastroenterology & Motility* 2019 ; 31 (S4) : e13671. Special issue: Abstract Supplement for NeuroGASTRO 2019 Congress, September 05-07, 2019, Lisbon, Portugal <https://doi.org/10.1111/nmo.13671>

JFHOD 2020 Abstract #000250

Titre

Intérêt de demander l'effet de bains d'eau chaude sur les vomissements

Auteurs

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Introduction

Le soulagement des vomissements par les bains ou douches d'eau chaude est un critère renforçant le diagnostic de syndrome cannabinoïde selon Rome IV. Ce comportement ayant également été décrit chez des patients souffrant du syndrome de vomissements cycliques ou du syndrome de nausées/vomissements chroniques¹, la question de son intérêt vis-à-vis du diagnostic du *cannabinoid hyperemesis syndrome* reste en suspens. Notre but était d'évaluer la sensibilité et la spécificité de la présence de ce comportement vis-à-vis de la consommation de cannabis dans une population se plaignant de vomissements sans substrat organique.

Patients et Méthodes

1.761 patients consécutifs présentant des symptômes digestifs hauts sans substrat organique ont complété un auto-questionnaire basé sur les critères de Rome IV entre décembre 2017 et février 2020. 320 patients souffrant de

vomissements chroniques ont été étudiés. La consommation de cannabis était établie sur base de la déclaration du patient, éventuellement complétée par une analyse urinaire ou sanguine dans certains cas. Il a également été demandé si les vomissements étaient améliorés par les bains ou douches chaud(e)s, et si ceux-ci ont un caractère cyclique. Les caractéristiques des patients ont également été analysées.

Résultats

Parmi les 320 patients se plaignant de vomissements chroniques, 111 (34,69%) remplissaient les critères de Rome IV pour le syndrome de vomissements cycliques, 14 (4,38%) étaient consommateurs de cannabis et 195 (60,93%) avaient des vomissements chroniques sans être consommateurs de cannabis.

Les consommateurs de cannabis étaient plus jeunes (âge moyen de 30,21 vs 47,20 ans, $p < 0,0001$) et avaient un BMI plus faible (21,66 vs 25,85 kg/m², $p = 0,0026$) que les non-consommateurs. La qualité de vie n'était pas différente chez les consommateurs de cannabis (GIQLI de 64,36 vs 74,91 points, $p = 0,054$). Le score d'anxiété-dépression était également identique (HADS : 21,00 vs 16,49 points, $p = 0,074$).

Sur l'ensemble des patients se plaignant de vomissements chroniques, 6 étaient soulagés par les bains chauds (1,88%). Les 6 patients soulagés par les bains chauds étaient tous consommateurs de cannabis (spécificité de 100%), sur un total de 14 patients (sensibilité de 42,86%). La valeur prédictive négative de ce comportement vis-à-vis de la consommation de cannabis était de 97,45% et la valeur prédictive positive de 100%. L'indice de Youden était de 0,43. Ce comportement était fortement associé à la consommation de marijuana (OR 468,8 [IC 95% = 24,37-9017,00], $p < 0,0001$). Les vomissements étaient cycliques dans une proportion similaire qu'il y ait ou non consommation de cannabis (50,00 vs 50,65% respectivement, $p > 0,99$).

Conclusion

Le soulagement des vomissements par des bains ou douches chaud(e)s doit faire suspecter une consommation de cannabis. Ce comportement doit rester un critère accessoire du diagnostic de vomissements liés au cannabis vu son manque de sensibilité. Une étude évaluant ce comportement chez un plus grand nombre de vomisseurs chroniques avec recherche systématique de cannabinoïdes

urinaires est souhaitable pour affiner la relation entre syndrome de vomissements cycliques et syndrome cannabinoïde.

Référence

(1) Venkatesan T, Sengupta J, Lodhi A, et al. An internet survey of marijuana and hot shower use in adults with cyclic vomiting syndrome. *Exp Brain Res* 2014 ; 232 (8) : 2563-2570.

POSTER presented on March 29, 2020 (P.488)

Intérêt de demander l'effet de bains d'eau chaude sur les vomissements

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Résumé

Introduction

Le soulagement des vomissements par les bains ou douches d'eau chaude est un critère reproductible de diagnostic de syndrome cannabinoïde selon Rome IV. Ce comportement peut également être décrit chez des patients souffrant du syndrome de vomissements cycliques ou du syndrome de malabsorption chronique. Le questionnement sur la sensibilité et la spécificité de ce diagnostic de syndrome cannabinoïde est d'autant plus important que la consommation de cannabis est une prévalence en augmentant de façon exponentielle.

Patients et méthodes

152 patients consécutifs présentant des symptômes digestifs hauts sans substrat organique ont complété un auto-questionnaire basé sur les critères de Rome IV entre décembre 2017 et février 2019. 122 patients souffrant de vomissements chroniques ont été exclus. La consommation de cannabis était évaluée sur la base du comportement du patient, d'entrevues complètes par une analyse urinaire ou sanguine dans certains cas. Il a également été demandé si les vomissements étaient associés aux bains ou douches chaud(e)s, et si oui ou non un arrêt ou une diminution des vomissements était associé à ces bains ou douches chaud(e)s.

Résultats

Parmi les 122 patients se plaignant de vomissements chroniques, 112 (91,6%) remplissaient les critères de Rome IV pour le syndrome de vomissements chroniques. 10 (8,4%) étaient consommateurs de cannabis et 108 (91,6%) avaient des vomissements chroniques sans consommation de cannabis. Les consommateurs de cannabis étaient plus jeunes (âge moyen de 30,33 vs 47,20 ans, $p = 0,0001$) et avaient un BMI plus faible (24,46 vs 26,78 kg/m², $p = 0,0001$) que les non-consommateurs. Le questionnaire de consommation de cannabis (100%) ou l'analyse urinaire (100%) ou sanguine (100%) ont confirmé la consommation de cannabis (100%) ou l'absence de consommation de cannabis (100%).

Sur l'ensemble des patients se plaignant de vomissements chroniques, 4 étaient soulagés par les bains chauds (3,28%). Les 4 patients soulagés par les bains chauds étaient tous consommateurs de cannabis (spécificité de 100%), sur un total de 14 patients (sensibilité de 28,57%). La valeur prédictive négative de ce comportement vis-à-vis de la consommation de cannabis était de 97,45% et la valeur prédictive positive de 100%. L'analyse de l'usage des bains chauds (100%) ou l'analyse de l'usage des bains chauds (100%) ont confirmé la consommation de cannabis (100%) ou l'absence de consommation de cannabis (100%).

Conclusion

Le soulagement des vomissements par les bains ou douches chaud(e)s doit faire suspecter une consommation de cannabis. Ce comportement doit rester un critère accessoire du diagnostic de vomissements liés au cannabis ou au syndrome de vomissements cycliques.

Abstract

The relief of vomiting by hot baths or showers is a reproducible criterion for diagnosis of cannabinoid syndrome according to Rome IV. This behavior can also be described in patients suffering from cyclic vomiting syndrome or chronic malabsorption syndrome. The questioning on the sensitivity and specificity of this diagnosis of cannabinoid syndrome is all the more important as cannabis consumption is increasing exponentially.

Patients and methods

152 consecutive patients presenting with upper digestive symptoms without organic substrate completed a questionnaire based on the Rome IV criteria between December 2017 and February 2019. 122 patients suffering from chronic vomiting were excluded. Cannabis consumption was evaluated on the basis of the patient's behavior, of interviews, of complete urinalysis or blood analysis in some cases. It was also asked if the vomiting was associated with hot baths or showers, and if yes or no a stop or decrease of vomiting was associated with these hot baths or showers.

Results

Among the 122 patients complaining of chronic vomiting, 112 (91.6%) fulfilled the Rome IV criteria for cyclic vomiting syndrome. 10 (8.4%) were cannabis consumers and 108 (91.6%) had chronic vomiting without cannabis consumption. Cannabis consumers were younger (mean age of 30.33 vs 47.20 years, $p = 0.0001$) and had a lower BMI (24.46 vs 26.78 kg/m², $p = 0.0001$) than non-consumers. The questionnaire on cannabis consumption (100%) or urinalysis (100%) or blood analysis (100%) confirmed cannabis consumption (100%) or the absence of cannabis consumption (100%).

Conclusion

The relief of vomiting by hot baths or showers should make one suspect cannabis consumption. This behavior should remain an accessory criterion for the diagnosis of vomiting related to cannabis or cyclic vomiting syndrome.

Keywords

Cyclic vomiting syndrome, chronic malabsorption syndrome, cannabinoid syndrome, hot baths, hot showers, cannabis consumption, Rome IV criteria.

References

(1) Wuestenberghs F, Melchior C, Desprez C, Leroi A, Gourcerol G. The relief of vomiting by hot baths or showers is a reproducible criterion for diagnosis of cannabinoid syndrome according to Rome IV. *Exp Brain Res* 2014; 232 (8) : 2563-70.

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Resumé

Le soulagement des vomissements par les bains ou douches chaud(e)s doit faire suspecter une consommation de cannabis. Ce comportement doit rester un critère accessoire du diagnostic de vomissements liés au cannabis ou au syndrome de vomissements cycliques.

Mots-clés

Syndrome de vomissements cycliques, syndrome de malabsorption chronique, syndrome cannabinoïde, bains chauds, douches chaudes, consommation de cannabis, critères de Rome IV.

References

(1) Wuestenberghs F, Melchior C, Desprez C, Leroi A, Gourcerol G. The relief of vomiting by hot baths or showers is a reproducible criterion for diagnosis of cannabinoid syndrome according to Rome IV. *Exp Brain Res* 2014; 232 (8) : 2563-70.

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Resumé

Le soulagement des vomissements par les bains ou douches chaud(e)s doit faire suspecter une consommation de cannabis. Ce comportement doit rester un critère accessoire du diagnostic de vomissements liés au cannabis ou au syndrome de vomissements cycliques.

Mots-clés

Syndrome de vomissements cycliques, syndrome de malabsorption chronique, syndrome cannabinoïde, bains chauds, douches chaudes, consommation de cannabis, critères de Rome IV.

References

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Resumé

Le soulagement des vomissements par les bains ou douches chaud(e)s doit faire suspecter une consommation de cannabis. Ce comportement doit rester un critère accessoire du diagnostic de vomissements liés au cannabis ou au syndrome de vomissements cycliques.

Mots-clés

Syndrome de vomissements cycliques, syndrome de malabsorption chronique, syndrome cannabinoïde, bains chauds, douches chaudes, consommation de cannabis, critères de Rome IV.

References

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Resumé

Le soulagement des vomissements par les bains ou douches chaud(e)s doit faire suspecter une consommation de cannabis. Ce comportement doit rester un critère accessoire du diagnostic de vomissements liés au cannabis ou au syndrome de vomissements cycliques.

Mots-clés

Syndrome de vomissements cycliques, syndrome de malabsorption chronique, syndrome cannabinoïde, bains chauds, douches chaudes, consommation de cannabis, critères de Rome IV.

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Introduction

Syndrôme d'hyperémèse cannabinoïde (*cannabinoid hyperemesis syndrome*) selon **Rome IV** (1):

Critères diagnostiques* :

1. Vomissements épisodiques stéréotypés ressemblant à un syndrome de vomissements cycliques (SVC) en termes d'apparition, durée et fréquence
2. Présentation après une utilisation excessive et prolongée de cannabis
3. Soulagement des épisodes de vomissement par arrêt prolongé de la consommation de cannabis

* Critères remplis au cours des 3 derniers mois avec symptôme apparu au moins 6 mois avant le diagnostic

Critère supportif :

Peut être associé à un comportement de bain pathologique (bains chauds ou douches prolongés).

Comportement également décrit chez des patients souffrant du SVC ou du syndrome de nausées/vomissements chroniques (2)

(1) V. Stanghellini et al. Gastrointestinal disorders. *Gastroenterology* 2016;150:1380-1392.

(2) Venkatesan T, Sengupta J, Lodhi A, et al. An internet survey of marijuana and hot shower use in adults with cyclic vomiting syndrome. *Exp Brain Res* 2014; 232 (8) : 2563-70.

But de l'étude

Evaluer la sensibilité et spécificité de la présence de ce comportement vis-à-vis de la consommation de cannabis dans une population se plaignant de vomissements sans substrat organique.

Méthodes

Patients consécutifs présentant des symptômes digestifs hauts sans substrat organique consultant dans le service de physiologie digestive

Recrutement entre décembre 2017 et juin 2019

Auto-questionnaire basé sur les critères de Rome IV
+ question sur l'amélioration des vomissements par les bains ou douches chaud(e)s
+ question sur le caractère cyclique des vomissements

Consommation de cannabis établie sur base de la déclaration du patient

Résultats

Tableau. Caractéristiques des patients selon la consommation ou non de cannabis

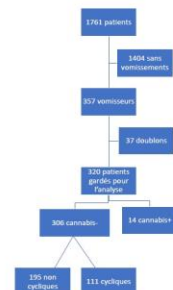
	Cannabis (-) (n = 306)	Cannabis + (n = 14)	valeur p
Âge médian (range)	47 (18-83)	28 (20-47)	< 0,0001
BMI moyen, kg.m ⁻² (± SD)	25,9 (± 5,8)	21,7 (± 4,3)	0,0026
Sex ratio Homme/Femme (%)	0,24 (80,4)	0,75 (57,1)	0,046
GIQLI score moyen (± SD)	74,9 (± 22,2)	64,36 (± 21,9)	0,054
HADS score moyen (± SD)	16,5 (± 7,72)	21,0 (± 9,3)	0,074
BMI: Body Mass Index, GIQLI: Gastrointestinal Quality of Life Index, HADS: Hospital Anxiety Depression Scale, SD: Standard Deviation			

Évaluation du comportement « bains ou douches chaud(e)s » :

- 6 patients soulagés parmi tous les vomisseurs (1,88%)
- Spécificité = 100% (tous consommateurs de cannabis)
- Sensibilité = 42,86% (sur tous les consommateurs de cannabis)
- Valeur Prédictive Négative = 97,45%
- Valeur Prédictive Positive = 100%
- Indice de Youden = 0,43

Comportement fortement associé à la consommation de cannabis
Odds ratio = 468,8 (IC 95% 24,37-9017,00), $p < 0,0001$

Pas d'intérêt du caractère cyclique des vomissements pour différencier les consommateurs de cannabis des non consommateurs
50,00 vs 50,65% respectivement, $p > 0,99$



Conclusion:

Le soulagement des vomissements par des bains ou douches chaud(e)s doit faire suspecter une consommation de cannabis. Ce comportement doit rester un critère accessoire du diagnostic de vomissements liés au cannabis ou au syndrome de vomissements cycliques.

Une étude évaluant ce comportement chez un plus grand nombre de vomisseurs chroniques avec recherche systématique de cannabinoïdes urinaires est souhaitable pour affiner la relation entre syndrome de vomissements cycliques et syndrome cannabinoïde.

Aucun conflit d'intérêt.
FW a reçu un soutien financier de la Fondation Mont-Godinne (Yvoir, Belgique) en 2018.

Résumé n°000250
Poster n°P-488

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JFHOD 2021 Abstract #000650

Titre

La qualité du sommeil et l'insomnie sont associées à la qualité de vie dans la dyspepsie fonctionnelle

Auteurs

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Introduction

Les troubles du sommeil sont fréquents dans la population générale et sont encore plus fréquents chez les patients atteints de dyspepsie fonctionnelle (DF) (Fass et al., 2000). Ils sont associés à la sévérité des symptômes, à des niveaux plus élevés d'anxiété et de dépression et à une diminution de la productivité au travail dans cette maladie (Lacy et al., 2011, Matsuzaki et al., 2018).

Nos objectifs étaient d'évaluer la relation entre le sommeil subjectif et la qualité de vie (QdV) et d'identifier les facteurs associés à une mauvaise qualité du sommeil dans la DF.

Patients et méthodes

1.220 patients adressés pour des troubles fonctionnels intestinaux dans un centre de soins tertiaires entre fin 2017 et juin 2019 ont été étudiés à l'aide d'auto-questionnaires. Parmi eux, 355 patients atteints de dyspepsie fonctionnelle selon

les critères de Rome IV ont été identifiés (sous-types : 63,9% PDS, 11,6% EPS et 24,5% chevauchement PDS + EPS). Le chevauchement avec le syndrome de l'intestin irritable (SII) a été défini selon les critères de Rome IV. Le sommeil a été évalué en utilisant à la fois l'indice de qualité du sommeil de Pittsburgh (PSQI) et l'indice de sévérité de l'insomnie (ISI). Une mauvaise qualité du sommeil a été définie comme un PSQI supérieur à cinq (89,6% de sensibilité et 86,5% de spécificité). L'insomnie était définie comme un score ISI supérieur ou égal à dix (86,1% de sensibilité et 87,7% de spécificité). La sévérité des symptômes dyspeptiques a été évaluée à l'aide d'un score composite sur les symptômes (TSS). La QdV a été évaluée par l'indice *GastroIntestinal Quality of Life Index* (GIQLI). Les niveaux d'anxiété et de dépression ont été évalués à l'aide de l'échelle *Hospital Anxiety and Depression Scale* (HADS). La vidange gastrique a été évaluée par un test respiratoire à l'acide ^{13}C -octanoïque dans un sous-groupe de patients. Le pyrosis était évalué à l'aide d'une échelle de Likert en 5 points.

Résultats

Les patients atteints de DF étaient majoritairement des femmes (76.6%). L'âge moyen des patients était de 46.9 ± 15.7 ans. Un chevauchement avec le SII était présent chez 44.8% des patients. Dans notre population de DF, 81.4% des patients avaient un sommeil de mauvaise qualité. Ces derniers étaient plus âgés (48.1 ± 15.4 vs 41.3 ± 16.0 ans, $p = 0.0009$), avaient une QdV plus altérée (GIQLI: 75.2 ± 18.4 vs 92.0 ± 15.4 , $p < 0.0001$), une plus grande sévérité de leurs symptômes digestifs (TSS: 18.9 ± 3.6 vs 17.2 ± 3.9 , $p = 0.0007$) et des scores d'anxiété et de dépression plus élevés (HADS: 17.7 ± 7.2 vs 11.8 ± 5.1 , $p < 0.0001$). Les autres paramètres étudiés, à savoir, l'indice de masse corporelle (IMC), le sexe, le tabagisme, la durée des symptômes dyspeptiques, la distribution des sous-types de dyspepsie, le chevauchement avec le SII, la présence de symptômes de reflux et la vidange gastrique étaient comparables dans les deux groupes ($p > 0.05$ pour tous). La qualité du sommeil était corrélée à la QdV ($r = -0.43$ [IC à 95% = -0.51 à -0.34], $p < 0.0001$; voir Figure). Les facteurs indépendants prédictifs d'une mauvaise qualité du sommeil étaient le score de dépression (OR 1.40 [IC à 95% = 1.08-1.81], $p = 0.012$) et la sévérité des symptômes dyspeptiques (OR 1.28 [IC à 95% = 1.02-1.62], $p = 0.036$). Une insomnie était retrouvée chez 60.6% des patients. Sa présence était associée à une moins bonne QdV, une plus grande

sévérité de leurs symptômes digestifs et des scores d'anxiété et de dépression plus élevés ($p < 0.001$ pour tous).

Conclusions

Nous avons trouvé une prévalence élevée de troubles du sommeil chez les patients souffrant de dyspepsie fonctionnelle, avec environ 80% d'entre eux ayant une mauvaise qualité de sommeil et 60% souffrant d'insomnie. La mauvaise qualité du sommeil et l'insomnie sont associées à une altération de la QdV, à une plus grande sévérité des symptômes et à des scores d'anxiété et de dépression plus élevés dans cette maladie.

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- MATSUZAKI, J., SUZUKI, H., TOGAWA, K., YAMANE, T., MORI, H., KOMORI, T., MASAOKA, T. & KANAI, T. 2018. Burden of impaired sleep quality on work productivity in functional dyspepsia. *United European Gastroenterol J*, 6, 398-406.

neuroGASTRO 2021 Abstract NGS15372-90

Title

Sleep quality and insomnia are associated with a lower quality of life in functional dyspepsia

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Background/Aims

Sleep disturbances are highly prevalent in patients with functional dyspepsia (FD) and are associated with worse symptom severity, anxiety, depression, and productivity at work in this disease. Our aims were to assess the relationship between subjective sleep and quality of life (QoL) and to identify factors associated with poor sleep quality in FD.

Methods

1,220 patients referred to our motility clinic between December 2017 and June 2019 were assessed using self-administered questionnaires: the TSS for the severity of symptoms, a 5-point Likert scale for heartburn, the GIQLI for GI-related QoL, the HADS for psychological distress, the PSQI for sleep quality and the ISI for insomnia. Functional dyspepsia and its overlap with irritable bowel syndrome (IBS) were defined according to the Rome IV criteria.

Key results

Among the total cohort, 355 patients with FD were identified (76.6% of women, mean age of 46.9 ± 15.7 years). Overlap with IBS was present in 44.8% of the patients. 81.4% had poor quality sleep; patients belonging to this subgroup were

older, had a more altered QoL, a greater severity of their digestive symptoms and higher anxiety and depression scores. Sleep quality and QoL were highly correlated ($r = -0.43$ [95% CI: -0.51 to -0.34], $p < 0.0001$). Independent factors predicting poor sleep quality were depression levels (OR 1.40) and the severity of dyspeptic symptoms (OR 1.28). Insomnia was found in 60.6% of the patients, with similar results.

Conclusions

We found a high prevalence of sleep disorders in patients suffering from functional dyspepsia. The presence of sleep disturbances was associated with altered QoL, higher severity of symptoms and higher psychological distress in this disease. Sleep quality and insomnia levels were correlated with GI-specific QoL.

Fabien Wuestenberghs, Chloé Melchior, Charlotte Desprez, Anne-Marie Leroi, Marie Netchitailo, Guillaume Gourcerol. Sleep quality and insomnia are associated with a lower quality of life in functional dyspepsia [neuroGASTRO abstract NGS15372-90]. *Neurogastroenterology & Motility* 2021 ; 33 (S2) : e14244. Special issue: Abstract Supplement for NeuroGASTRO 2021 Congress, September 02-04, 2021 <https://doi.org/10.1111/nmo.14244>

DDW 2021 Abstract #Sa391

Title

Sleep disorders are associated with a lower quality of life in functional dyspepsia

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Background/Aims

Sleep disorders are common in the general population and are even more frequent in patients with functional dyspepsia (FD) (1). Sleep disorders are associated with the severity of gastrointestinal (GI) symptoms, psychological distress, and decreased productivity at work in FD (2,3). Our aims were to identify factors associated with sleep disorders in FD and assess the relationship with quality of life (QoL).

Methods

We assessed 1,220 patients referred to the motility clinic in our tertiary care center between December 2017 and June 2019. Overlap with irritable bowel syndrome (IBS) was defined according to the Rome IV criteria. The severity of GI symptoms (TSS), heartburn (5-point Likert scale), QoL (GIQLI), psychological

distress (HAD), sleep quality (PSQI) and the insomnia (ISI) were assessed using self-questionnaires. A poor sleep quality was defined as a PSQI > 5 while insomnia was defined as an ISI $\geq$ 10. Gastric emptying was assessed by a 13C-octanoic acid breath test.

Key results

Among the 1,220 patients assessed by questionnaires, 355 patients had a diagnose of FD according to Rome IV (subtypes: 63.9% of postprandial distress syndrome, 11.6% of epigastric pain syndrome and 24.5% of overlap). Patients with FD were mainly women (76.6%) with a mean age of 46.9 ± 15.7 years. Overlap with IBS was present in 44.8% of FD patients. In our FD population, 81.4% of patients had poor quality sleep. In this subgroup, quality of life was lower and overall symptoms were more severe (see Table, reporting results for other studied parameters). The quality of sleep was correlated with QoL ($r = -0.43$ [95% CI: -0.51 to -0.34], $p < 0.0001$; see Figure). Using logistic regression, independent factors predicting poor sleep quality were depression levels (OR 1.40 [95% CI: 1.08-1.81], $p = 0.012$) and the severity of dyspeptic symptoms (OR 1.28 [95% CI: 1.02-1.62], $p = 0.036$). Insomnia was found in 60.6% of FD patients with similar results.

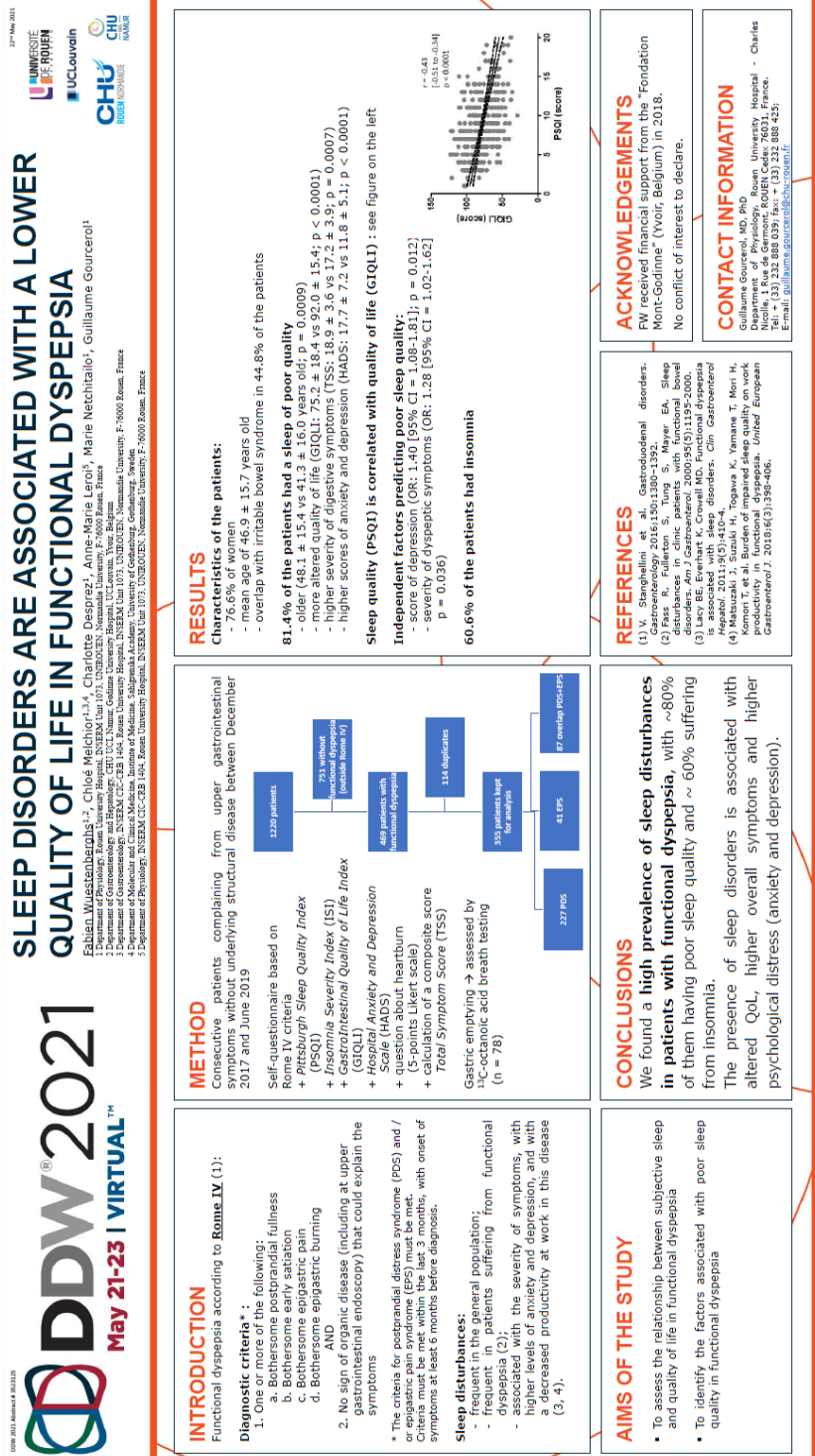
Conclusions

A subgroup of FD suffered from sleep disorders. The presence of sleep disorders is associated with altered QoL, higher overall symptoms and higher psychological distress. The identification of those patients could lead to better management of FD.

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Fabien Wuestenberghs, Chloé Melchior, Charlotte Desprez, Anne-Marie Leroi, Marie Netchitailo, Guillaume Gourcerol. Sa391 Sleep disorders are associated with a lower quality of life in functional dyspepsia [DDW abstract Sa391]. *Gastroenterology* 2021 ; 160 (6) : S-488. [https://doi.org/10.1016/S0016-5085\(21\)01873-4](https://doi.org/10.1016/S0016-5085(21)01873-4)



Invited review on pyloric distensibility

Title

Pyloric distensibility in health and disease

Authors' names

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Abstract

Until recently, gastric motility measurements in Humans were mostly limited to accommodation (using barostat or 3-dimensional imaging studies of gastric volume) and gastric emptying tests, the latter being the only one performed in routine clinical care. Accurate and easy to use techniques were lacking to assess pyloric function in health and disease. Recently, pyloric distensibility has been developed and validated to assess pyloric opening. Several studies confirmed that pyloric distensibility was decreased in gastroparesis and correlated with gastric emptying as well as gastroparesis symptoms. In addition, pyloric distensibility may predict outcome of endoscopic techniques targeting the pylorus, namely intra-pyloric botulinum toxin injection and gastric per-oral pyloromyotomy. Pyloric distensibility appears therefore to be a promising and useful new tool in the workup of gastroparesis patients.

Fabien Wuestenberghs and Guillaume Gourcerol. Pyloric distensibility in health and disease. *American Journal of Physiology-Gastrointestinal and Liver Physiology* 2021 ; 321 (2) : G133-G138. <https://doi.org/10.1152/ajpgi.00460.2020>

This paper has been cited 5 times [ consulted on March 17, 2023].

The Altmetric score is 2 [ consulted on March 17, 2023].

UEG Week 2022 Abstract #AS-UEG-2022-02097

Title

Prevalence and impact of migraine headaches in Rome IV-based functional dyspepsia

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Background/Aims

Migraine headaches are associated with functional dyspepsia (FD) according to Rome IV criteria in the general population (prevalence of 43.6 vs 20.0% in controls, OR 3.1 [95% CI: 2.2-4.3], $p < 0.005$) (1). Indeed, common pathophysiological mechanisms have been reported in both disorders, especially alterations of the gut-brain axis (2). Furthermore, patients with uninvestigated dyspepsia referred for an upper gastrointestinal endoscopy frequently have migraine headaches (3). Our aim was therefore to assess the impact of the overlap with migraine in patients with FD.

Methods

Consecutive patients with investigated dyspepsia were assessed with self-administered questionnaires. Functional dyspepsia, its subtypes postprandial

distress syndrome (PDS) and epigastric pain syndrome (EPS), and irritable bowel syndrome (IBS) were diagnosed according to Rome IV criteria. Self-reported migraine was assessed by questioning patients for migraine headaches. Patients were also asked if they had fibromyalgia. Quality of life (QoL) was assessed by the *Gastrointestinal Quality of Life Index* (GIQLI). Anxiety and depression levels were evaluated using the *Hospital Anxiety and Depression* (HAD) scale. Sleep was assessed using both the *Pittsburgh Sleep Quality Index* (PSQI) and the *Insomnia Severity Index* (ISI). Gastric half-emptying time was assessed using octanoic acid breath testing.

Results

355 patients with Rome IV-based FD were identified. Overlap with migraine was present in 134 of the patients (37.7%). In univariate analysis, this comorbidity was associated with better QoL (GIQLI: 74.1 ± 18.6 vs 80.9 ± 18.9 points, $p = 0.0011$), increased overlaps with IBS (52.2 vs 40.3%, $p = 0.036$), fibromyalgia (12.7 vs 5.9%, $p = 0.031$) and insomnia (70.9 vs 54.3%, $p = 0.0024$), and a longer duration of FD (98.0 ± 109.8 vs 62.9 ± 90.9 months, $p = 0.0011$). On the contrary, overlap with migraine did not alter age, body mass index, sex distribution, gastric half-emptying time, HADS score, FD subtypes distribution, and sleep quality ($p > 0.05$ for all). In multivariate analysis, independent predictors of the overlap with migraine in FD patients were FD duration (OR 1.003 [95% CI: 1.001-1.006], $p = 0.0044$) and the presence of insomnia (OR 1.66 [95% CI: 1.01-2.76], $p = 0.047$).

Conclusions

Migraine headaches affect more than one third of patients suffering from functional dyspepsia. Overlap with migraine is independently associated with a longer duration of the disorder and with the presence of insomnia.

Keywords

Functional dyspepsia; overlap syndromes; migraine

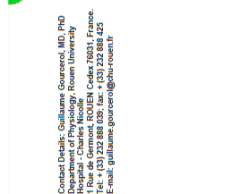
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Migraine headaches are associated with functional

Aims & Methods

Our aim was therefore to assess the impact of the overlap with migraine in patients with FD.

Consecutive patients with investigated dyspepsia between end of 2017 and June 2019 at Rouen hospital were assessed with self-administered questionnaires. FD, its subtypes postprandial distress syndrome (PDS) and epigastric pain syndrome (EPS), and irritable bowel and epigastric pain syndrome (EPS), and irritable bowel syndrome (IBS) were diagnosed according to Rome IV criteria. Self-reported migraine was assessed by questioning patients. Patients were also asked if they had had a myocardial infarction (MI), a stroke, or a heart failure (HF).

The Gastrointestinal Quality of Life Index (GIQLI), Anxiety and Depression levels were evaluated using the Hospital Anxiety and Depression scale (HADS). Sleep quality was assessed both with the Pittsburgh Sleep Quality Index (PSQI) and the Epworth Sleepiness Scale (ESS). Gastric half-emptying time was assessed in a subgroup of patients using octanoic acid breath testing. All statistical analyses were performed using GraphPad Prism 9 form (Statistics 64-bit, Version 9.4.1 (681)).

	Migrate (n = 134)	No migrate (n = 221)	p-value
Mean age, years (± SD)	45.4 (± 15.6)	47.8 (± 15.9)	0.15
Mean BMI, kg/m ² (± SD)	24.0 (± 5.1)	24.2 (± 5.2)	0.99
Sex ratio Male/Female (% males)	0.23 (18.7)	0.36 (26.2)	0.12
GDXL mean score (± SD)	74.1 (± 18.6)	80.9 (± 18.9)	0.0011
HADS, mean score (± SD)	17.1 (± 7.9)	16.3 (± 6.8)	0.59
HADS-A, mean subscore (± SD)	10.3 (± 4.6)	9.7 (± 4.0)	0.26
HADS-D, mean subscore (± SD)	6.7 (± 4.3)	6.6 (± 3.9)	0.97
PSQI, mean score (± SD)	9.6 (± 3.9)	8.5 (± 3.7)	0.012
Poor sleep quality, n (%)	115 (85.8)	174 (78.7)	0.12
ISI, mean score (± SD)	13.3 (± 6.4)	10.7 (± 6.2)	0.0002
Insomnia, n (%)	95 (70.9)	120 (54.3)	0.0024
Overlap with IBS, n (%)	70 (52.2)	89 (40.3)	0.036
Overlap with fibromyalgia, n (%)	17 (12.7)	13 (5.9)	0.031
PDS subtype, n (%)	88 (65.7)	139 (62.9)	0.65
EPS subtype, n (%)	10 (7.5)	31 (14.0)	0.096
EPS+PEPS subtype, n (%)	36 (26.9)	51 (23.1)	0.45
FD duration, months (± SD)	98.0 (± 109.8)	62.9 (± 90.9)	0.0011
Free time, minutes (± SD)	162.0 (± 49.9)*	165.6 (± 64.2)*	0.96

355 patients with Rome IV-based FD were identified. Overlap with migraine was present in 134 of the patients (37.7%). In univariate analysis (see Table 1), a comorbidity was associated with better QoL (GQI, 74.1 ± 18.6 vs. 68.0 ± 18.9 points, $p = 0.001$), increased overlaps with IBS (52.2% vs. 40.3%, $p = 0.003$), bloating (12.7% vs. 5.9%, $p = 0.031$) and insomnia (70.9% vs. 62.9%, $p = 0.004$), and a longer duration of FD (98.0 ± 109.8 h, 62.9 ± 90.9 g, $p = 0.001$). On the contrary, overlap with migraine did not alter age, gender, body mass index, constipation, gastric full-emptying time, HADS score, FD subtypes distribution, and sleep quality ($p > 0.05$ for all). In multivariate analysis, independent predictors of the overlap with migraine in FD patients were FD duration (OR 1.003 [95% CI = 1.001-1.006]; $p = 0.0044$) and the presence of insomnia (OR 1.62 [95% CI = 1.01-2.61]; $p = 0.047$).

Conclusion
Migraine headaches affect more than one third of patients suffering from functional dyspepsia. Overlap with migraine is independently associated with a longer duration of the disorder and with the presence of insomnia.

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Index

A

abuse · - 14 -, - 39 -, - 40 -, - 42 -, - 46 -, - 68 -,
- 106 -, - 109 -, - 110 -, - 111 -, - 136 -, -
137 -, - 254 -, - 343 -, - 344 -
accommodation · - 9 -, - 10 -, - 12 -, - 13 -, -
17 -, - 18 -, - 20 -, - 29 -, - 31 -, - 40 -, - 45 -,
- 75 -, - 256 -, - 261 -, - 337 -, - 529 -
acetic acid · - 255 -, - 286 -, - 288 -, - 289 -, -
290 -, - 291 -, - 292 -, - 293 -, - 294 -, - 295
-, - 296 -, - 338 -
animal model · - 77 -, - 345 -
anterior cingulate cortex · - 56 -, - 57 -, - 59 -
anxiety · - 9 -, - 13 -, - 15 -, - 16 -, - 18 -, - 29 -,
- 39 -, - 40 -, - 43 -, - 44 -, - 46 -, - 48 -, - 59
-, - 60 -, - 62 -, - 69 -, - 77 -, - 89 -, - 94 -, -
104 -, - 106 -, - 108 -, - 111 -, - 128 -, - 130
-, - 132 -, - 144 -, - 146 -, - 148 -, - 163 -, -
165 -, - 169 -, - 171 -, - 173 -, - 174 -, - 176
-, - 190 -, - 193 -, - 201 -, - 216 -, - 223 -, -
235 -, - 237 -, - 238 -, - 243 -, - 247 -, - 248
-, - 249 -, - 250 -, - 253 -, - 260 -, - 264 -, -
267 -, - 340 -, - 341 -, - 343 -, - 478 -, - 512
-, - 513 -, - 523 -, - 524 -

B

belching · - 3 -, - 6 -, - 8 -, - 30 -, - 100 -, - 139 -
-, - 146 -, - 164 -, - 189 -, - 196 -, - 212 -, -
237 -, - 245 -, - 247 -, - 337 -, - 494 -
bladder pain syndrome · - 105 -, - 147 -, - 235
-, - 236 -, - 243 -, - 493 -
breath test · - 25 -, - 212 -, - 214 -, - 223 -, -
526 -

C

calcitonin gene-related peptide · - 50 -, - 54 -,
- 67 -, - 68 -, - 73 -, - 75 -, - 267 -, - 327 -, -
347 -
cannabis · - 187 -, - 200 -, - 202 -, - 515 -, -
516 -
central sensitisation · - 18 -, - 33 -, - 39 -, - 64
-, - 66 -, - 68 -, - 69 -, - 73 -, - 74 -, - 106 -, -
139 -, - 277 -, - 296 -, - 297 -, - 300 -, - 326
-, - 345 -, - 347 -
cholecystokinin · - 60 -, - 78 -, - 260 -
chronic nausea and vomiting syndrome · - 8 -
-, - 189 -, - 192 -, - 195 -, - 198 -, - 199 -, -
478 -, - 479 -
coeliac disease · - 20 -, - 22 -, - 94 -, - 117 -, -
144 -, - 164 -, - 188 -, - 344 -
colorectal distension · - 46 -, - 56 -, - 322 -
constipation · - 8 -, - 16 -, - 32 -, - 44 -, - 45 -, -
76 -, - 100 -, - 103 -, - 127 -, - 176 -, - 341 -, -
345 -
convergence · - 65 -, - 66 -, - 67 -, - 256 -, -
297 -, - 347 -
coping · - 17 -, - 42 -, - 343 -
cross-organ sensitisation · - 47 -, - 64 -, - 65 -,
- 67 -, - 70 -, - 73 -, - 74 -, - 79 -, - 82 -, -
249 -, - 256 -, - 257 -, - 258 -, - 277 -, - 278
-, - 297 -, - 299 -, - 300 -, - 309 -, - 310 -, -
326 -, - 327 -, - 328 -, - 329 -, - 338 -, - 339
-, - 347 -
cyclic vomiting syndrome · - 8 -, - 187 -, - 189
-, - 236 -, - 239 -

Index

D

depression · - 9 -, - 13 -, - 15 -, - 16 -, - 18 -, - 32 -, - 35 -, - 39 -, - 40 -, - 41 -, - 44 -, - 46 -, - 48 -, - 62 -, - 89 -, - 94 -, - 106 -, - 111 -, - 131 -, - 132 -, - 144 -, - 146 -, - 148 -, - 163 -, - 165 -, - 169 -, - 171 -, - 172 -, - 173 -, - 174 -, - 175 -, - 176 -, - 190 -, - 193 -, - 198 -, - 200 -, - 201 -, - 212 -, - 216 -, - 223 -, - 235 -, - 237 -, - 238 -, - 243 -, - 247 -, - 248 -, - 249 -, - 250 -, - 253 -, - 267 -, - 340 -, - 341 -, - 343 -, - 478 -, - 511 -, - 512 -, - 513 -, - 523 -, - 524 -, - 526 -, - 532 -

diabetes · - 18 -, - 19 -, - 20 -, - 94 -, - 113 -, - 139 -, - 144 -, - 164 -, - 188 -, - 214 -, - 216 -, - 221 -, - 223 -, - 236 -, - 239 -, - 337 -, - 344 -

dorsal root · - 49 -, - 50 -, - 66 -, - 67 -, - 70 -, - 75 -, - 297 -

E

eating disorder · - 42 -, - 106 -

F

fatigue · - 18 -, - 34 -, - 35 -, - 44 -, - 46 -, - 47 -, - 48 -, - 105 -, - 127 -, - 148 -, - 165 -, - 168 -, - 267 -, - 335 -

fibromyalgia · - 18 -, - 33 -, - 34 -, - 39 -, - 48 -, - 94 -, - 139 -, - 147 -, - 190 -, - 193 -, - 194 -, - 333 -, - 335 -, - 532 -

fMRI · - 13 -, - 263 -

FODMAP · - 16 -, - 256 -, - 509 -

fractalkine · - 71 -, - 72 -, - 278 -, - 282 -, - 289 -, - 290 -, - 298 -

G

gastroparesis · - 18 -, - 19 -, - 20 -, - 31 -, - 32 -, - 42 -, - 76 -, - 94 -, - 149 -, - 187 -, - 201 -, - 211 -, - 212 -, - 222 -, - 225 -, - 337 -, - 529 -

gluten · - 22 -, - 98 -, - 344 -

GORD · - 3 -, - 10 -, - 14 -, - 15 -, - 18 -, - 28 -, - 29 -, - 44 -, - 45 -, - 89 -, - 100 -, - 104 -, - 123 -, - 146 -, - 175 -, - 215 -, - 216 -, - 217 -, - 219 -, - 235 -, - 333 -, - 334 -, - 336 -, - 341 -, - 483 -, - 484 -, - 488 -

H

H. pylori · - 3 -, - 5 -, - 9 -, - 14 -, - 18 -, - 19 -, - 21 -, - 76 -, - 78 -, - 79 -, - 92 -, - 93 -, - 94 -, - 114 -, - 115 -, - 139 -, - 144 -, - 164 -, - 188 -, - 236 -, - 257 -

headaches · - 33 -, - 35 -, - 104 -, - 191 -, - 193 -, - 198 -, - 202 -, - 531 -, - 532 -

hypermobility · - 24 -, - 97 -, - 122 -

I

insomnia · - 41 -, - 106 -, - 133 -, - 147 -, - 163 -, - 165 -, - 166 -, - 168 -, - 169 -, - 171 -, - 172 -, - 173 -, - 174 -, - 176 -, - 201 -, - 235 -, - 237 -, - 238 -, - 243 -, - 474 -, - 523 -, - 524 -, - 526 -, - 532 -

M

MAPK · - 69 -, - 72 -, - 73 -, - 255 -, - 283 -, - 292 -, - 293 -, - 294 -, - 296 -, - 297 -, - 298 -, - 300 -, - 316 -, - 324 -, - 325 -, - 326 -, - 327 -, - 329 -, - 338 -, - 347 -

microbiota · II, - 1 -, - 12 -, - 59 -, - 60 -, - 256 -, - 267 -, - 328 -, - 347 -, - 349 -, - 509 -

microglia · - 52 -, - 71 -, - 72 -, - 73 -, - 74 -, -
82 -, - 257 -, - 283 -, - 297 -, - 299 -, - 327 -,
- 328 -, - 339 -

migraine · - 18 -, - 33 -, - 35 -, - 94 -, - 104 -, -
105 -, - 127 -, - 147 -, - 190 -, - 191 -, - 193
-, - 194 -, - 198 -, - 202 -, - 333 -, - 335 -, -
336 -, - 531 -, - 532 -

minocycline · - 72 -, - 283 -, - 290 -, - 291 -, -
292 -, - 297 -, - 311 -, - 322 -, - 323 -, - 327
-, - 328 -, - 345 -

N

NK1R · - 60 -, - 283 -, - 292 -, - 294 -, - 295 -, -
298 -, - 316 -, - 326 -, - 327 -, - 338 -, - 507
-

O

overactive bladder · - 36 -, - 44 -, - 104 -, -
127 -, - 235 -

P

permeability · - 12 -, - 16 -, - 46 -, - 71 -, - 266
-, - 267 -, - 268 -, - 269 -, - 277 -, - 509 -

PTSD · - 33 -, - 42 -, - 45 -, - 46 -, - 106 -, - 255
-

R

Rome criteria · - 4 -, - 6 -, - 8 -, - 14 -, - 20 -, -
30 -, - 81 -, - 94 -, - 143 -, - 144 -, - 146 -, -
187 -, - 190 -, - 191 -, - 192 -, - 193 -, - 197
-, - 199 -, - 222 -, - 238 -, - 243 -, - 247 -, -
333 -, - 511 -, - 512 -

rumination · - 8 -, - 29 -, - 31 -, - 100 -, - 188 -,
- 236 -, - 239 -, - 335 -

S

satiation · - 3 -, - 6 -, - 7 -, - 10 -, - 16 -, - 17 -, -
61 -, - 89 -, - 146 -, - 163 -, - 164 -, - 187 -, -
189 -, - 196 -, - 197 -, - 200 -, - 334 -, - 337
-

SIBO · - 25 -, - 94 -, - 117 -, - 334 -

somatisation · - 13 -, - 18 -, - 35 -, - 39 -, - 41 -
, - 46 -, - 62 -, - 94 -, - 106 -, - 111 -, - 134 -,
- 145 -, - 174 -, - 175 -, - 250 -, - 336 -, -
340 -, - 343 -, - 344 -

spinal cord · - 49 -, - 51 -, - 52 -, - 53 -, - 54 -, -
55 -, - 57 -, - 58 -, - 59 -, - 65 -, - 66 -, - 67 -,
- 68 -, - 72 -, - 74 -, - 256 -, - 279 -, - 281 -, -
282 -, - 283 -, - 289 -, - 290 -, - 293 -, - 294
-, - 295 -, - 296 -, - 297 -, - 298 -, - 313 -, -
315 -, - 316 -, - 324 -, - 325 -, - 326 -, - 327
-, - 328 -, - 338 -, - 339 -, - 507 -

V

vagus nerve · - 13 -, - 49 -, - 53 -, - 54 -, - 76 -,
- 77 -, - 312 -, - 329 -

visceral hypersensitivity · - 1 -, - 9 -, - 11 -, -
20 -, - 40 -, - 45 -, - 46 -, - 47 -, - 48 -, - 55 -,
- 59 -, - 62 -, - 63 -, - 64 -, - 70 -, - 72 -, - 73
-, - 77 -, - 82 -, - 225 -, - 253 -, - 254 -, - 255
-, - 256 -, - 257 -, - 258 -, - 259 -, - 264 -, -
296 -, - 297 -, - 298 -, - 309 -, - 323 -, - 326
-, - 328 -, - 329 -, - 337 -, - 338 -, - 347 -, -
509 -

W

western blot · - 269 -

