Sniffin' odors in the aging population? Smells like a new way to predict postoperative outcome!

Victoria Van Regemorter, MD

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Jury:

Promoter: Prof. Caroline Huart, MD, PhD (UCL)

Co-Promoter: Prof. André Mouraux, MD, PhD (UCL)

President: Prof. Bernard Hanseeuw, MD, PhD (UCL)

Prof. Mona Momeni, MD, PhD (UCL)

Prof. Marie de Saint-Hubert, MD, PhD (UCL)

Prof. Philippe Rombaux, MD, PhD (UCL)

Prof. Naïma Deggouj, MD (UCL)

Prof. Marie-Agnès Docquier, MD, PhD (UCL)

Prof. Thomas Hummel, MD (University of Dresden)

Prof. Vincent Bonhomme, MD, PhD (ULg)

Université catholique de Louvain (UCL)

Institute of Neuroscience (IoNS)

Fond de la Recherche Scientifique (F.R.S.-FNRS)

Dear Reader,

Every day of our lives, we encounter all sorts of odors and perfumes. A fragrance is composed of three chords – the head, the heart, and the base – each being composed of 4 essences or notes, just like a music melody. Fulfilling this four-year research mission would not have been possible without me being exposed, day to day, to a magical one-of-a-kind perfume.

The ***first*** note of this sweet-smelling melody comes from Caroline Huart, the mother of this project, my brilliant promoter. Mastering olfactory function like anybody else, she made me discover the fabulous power of this sense and gave me this incredible opportunity to study it within my beloved perioperative world. Speaking of the world, my best memory will remain forever our funny, endless – and sometimes deep – conversations we had in Bonita Springs, along with the smell of one – and sometimes more than one – freshly shaken cocktail. ***Merci tellement Caro.***

The ***second*** note is given by André Mouraux, my co-promoter, always carrying the wisest advice in his pocket and willing to help me improve my article manuscripts.

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with the team every single day, we share our experiences with the team, and, in the end, we spend most of our time with this team. I have spent the last four years among incredible coworkers. Some of them have become something between friendship and family. Et, aussi, LONGUE VIE au *Bureau Du Fond et à mes deux colocataires d'amour, Dieu et Lolo <3*.

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The ***ninth*** note is a pretty old note, which has laid the foundations of my researcher side. When I was 18, I was welcomed into the laboratory of Marie-Christine Many and Benoît Lengelé. With a lot of kindness and patience, they allowed me to make my first baby steps in this big galaxy that is scientific research. Antoine Christiaens, Lancelot Marique and Julie Craps were also part of the team. Lancelot, *mon cochercheur*, is one of my oldest friends, who also happens to be now a wonderful surgeon with whom I enjoy working even – and mostly – during a hEPatocytIC night.

The ***tenth*** note comes from my friends. They say friends are the family you choose. Friends have been an essential support and I am so grateful for every single person having walked part of the way with me during these four years. There are countless ways of connecting between humans, and still, each

friendship may add its own grain of sand. MERCI à VOUS TOU·T·E·S. *Et, à Mimi, Coco et Baba, vous êtes des humain·e·s exceptionnel·le·s.*

The ***eleventh*** note is given by my forever LOVING family without whom I would not have achieved the slightest bit of what I have been able to accomplish in my life. My grandparents, my parents, my siblings. I owe my Mom and Dad everything. They have supported me in every challenge I had to overcome and have loved me every minute of my life. My parents also offered me the precious chance to have a wonderful little brother, Elliott, and a truly amazing little sister, Lindsay, who have both always been present for me. I am profoundly proud of them. I love you to the moon and back, my Family.

The ***twelfth*** note … is the most special and unique one cause it's a part of me and of her dad, Quentin. The final and vital note. Alice, my baby, my sweet little girl, ma chose d'amour, Coeur, ALICENON! She is the most beautiful, smiling, and loving creature on earth. Also, she has this extraordinary power of detecting the smell of chocolate from miles away. Alice is my everything and makes me immensely proud to be her mom. Je t'aime tellement, Alice.

These 12 notes were a perfect blend of odors, weren't they?

I sincerely hope you will enjoy flipping through these pages,

"Don't let anyone rob you of your imagination, your creativity, or your curiosity. It's your place in the world; it's your life. Go on and do all you can with it, and make it the life you want to live."

Mae Jemison

Engineer, Physician, NASA astronaut

First African American woman to travel into space

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LIST OF ABBREVIATIONS

AD: Alzheimer's Disease

ApoE: Apolipoprotein E

ASA: American Society of Anesthesiologists

OB: Olfactory bulb

BMI: Body mass index

CAM: Confusion Assessment Method

CC index: Charlson Comorbidity index

CI: Confidence interval

CDT: Clock Drawing Test

CFS: Clinical Frailty Scale

COVID-19: Coronavirus Disease 2019

EFS: Edmonton Frail Scale

GA: General anesthesia

HADS: Hospital Anxiety and Depression Scale

HR: Hazard ratio

MCI: Mild cognitive impairment

MMSE: Mini-Mental State Examination

MoCA: Montreal Cognitive Assessment

NPV: Negative predictive value

OI: Olfactory impairment

OR: Odds ratio

PD: Parkinson’s disease

PND: Postoperative neurocognitive disorder

PPV: Positive predictive value

ROC: Receiving operator characteristic

SCC: Subjective cognitive concerns

SS: Sniffin’ Sticks test

TDI: Threshold Discrimination Identification

TL: Telomere length

T-MoCA: Telephone version of the MoCA

SECTION 1 –

BACKGROUND

Chapter 1. Aims of the present thesis

Olfactory dysfunction has been linked with increased mortality in the aging population, yet the exact reasons behind this are unclear. In parallel, effectively detecting vulnerable patients who will evolve poorly after surgery remains a complex task for the anesthesiologist. The main goals of this thesis were, first, to evaluate whether olfactory dysfunction could be a reliable predictor of poor postoperative outcome in older patients and, second, to identify the potential underpinning mechanisms linking olfactory impairment and increased death, notably by investigating the connection with frailty, cognition, and telomere length.

To this end, we established four specific objectives, as illustrated in **Figure 1.1**.:

(1) Correlating olfactory function with frailty.
(2) Exploring the perioperative association between olfactory function and cognitive function.
(3) Exploring the association between olfactory function and telomere length.
(4) Correlating preoperative olfactory function with postoperative morbidity and mortality.

This thesis is structured in four sections, with the two middle sections exposing our research results. The ***first*** section aims to lay the foundation for our multifaceted research project. The ***second*** and largest section examines the intricate relationships between olfactory dysfunction, frailty status, cognitive function, and, also, morbidity and mortality within the perioperative setting. We have split this section into two parts, firstly presenting promising findings from a preliminary “real-life” trial and secondly, strengthening our hypotheses with a more thorough and extensive approach. The ***third*** section addresses the link between smell and leukocyte telomere length within the presumed framework of biological aging. In the ***fourth*** section, we propose a new angle on what we

believe – from the depths of our scientific soul – makes the bridge between olfactory impairment and death. We end this thesis by discussing the place of olfactory function testing in tomorrow's perioperative world.

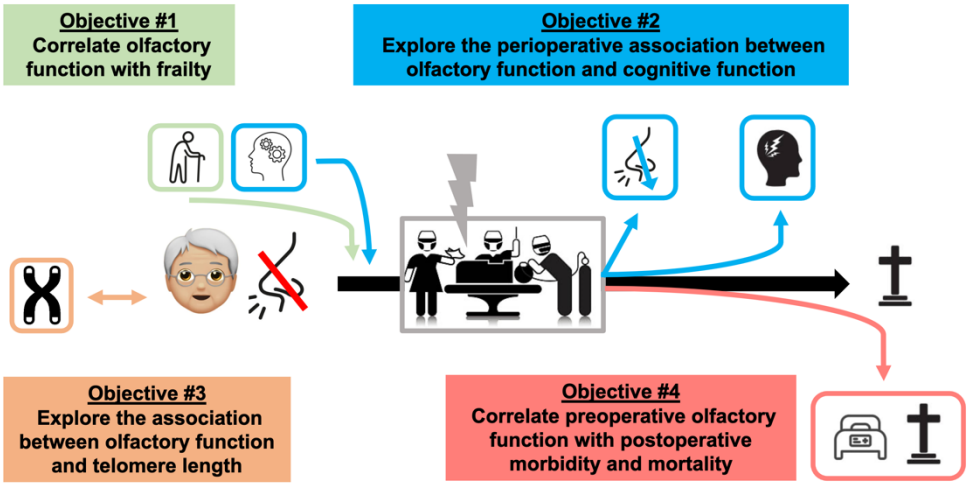

Figure 1.1. Illustration of the specific objectives of the present thesis

Chapter 2. The sense of olfaction

What, why, who?

As COVID-19 began to hit in 2020 all around the world, the sense of smell was suddenly put under the spotlight for the very first time. Indeed, looking back a few months before, in 2019, smell was ranked – unfairly – as only the sixth most valuable sense after sight, hearing, balance, touch, and taste by UK adults from the general public [1]. Yet, in our daily human life, olfaction plays a role in three major classes of function: eating behavior, environmental hazard avoidance, and social communication [2]. Not being able to smell correctly may thus have numerous consequences, including a reduced quality of life [3]. Imagine yourself eating your favorite dish without being able to perceive its entire "smellscape". Or not having this sudden flashback when smelling a familiar odor from our past. Of note, humans may discriminate more than one trillion (i.e., 10^{12}) olfactory stimuli, significantly outperforming the several millions of different colors an eye can see [4].

However, just as any other body function, olfaction may be defective, making us either partially (hyposmic) or totally (anosmic) unable to perceive odors. Alongside quantitative disorders relating to the intensity of odors, olfactory dysfunction may also present as qualitative – and most of the time, unpleasant – troubles: phantosmia, in which one may have the sensation of smelling an odor that is, in fact, absent, or parosmia which alters the quality of scents. Paradoxically, some people may suffer from an increased perception of odors, called hyperosmia [5].

What are the causes leading to olfactory impairment? A good way to apprehend the different etiologies would be first to retrace the path of an odor. Peripherally, odorant molecules are breathed into the nose and, thanks to the nasal turbinates, are directed towards the olfactory cleft, where lies the olfactory

neuroepithelium (**Figure 1.2.**). The latter then projects through the cribriform plate into the olfactory bulb [6]. The axons coming out of the olfactory bulb project to a certain number of central structures called the “primary olfactory cortex”, including the piriform cortex and the entorhinal cortex [7]. Finally, the secondary olfactory cortex comprises the thalamus, the hypothalamus, the hippocampus, the orbito-frontal cortex, and the insular cortex [8]. From this summarized approach to the actual – and far more complex – process of olfaction, we may understand the roles of both peripheral and/or central causes of olfactory disorders. The top three most frequent etiologies are post-traumatic (any craniocerebral trauma), post-infectious events, as well as sino-nasal diseases [9]. Any viral organism present in upper respiratory tract infections may be responsible for a decline in olfaction [5]. Of course, the past few years have shown the perfect example with SARS-CoV-2, the causal agent of COVID-19, provoking sudden loss of smell as a typical symptom in most infected patients. In this case, mechanisms of anosmia seem both peripheral and central, primarily due to neuronal and non-neuronal tissue damage and inflammation [10]. Sino-nasal diseases, such as chronic rhinosinusitis and nasal polyposis, constitute a peripherally mediated cause of olfactory dysfunction [11]. Importantly, olfactory impairment may affect patients suffering from a variety of neurological or psychiatric illnesses, such as neurodegenerative diseases, including especially Parkinson’s disease and Alzheimer’s disease (see Introduction in Section 1 Chapter 2), epilepsy, or depression [11][5]. Also, olfactory dysfunction may be the consequence of congenital disorders, drug- or toxin-induced causes, idiopathic causes, and last but not least, aging [5]. Quite a few hypotheses have been drawn to explain this age-related decline of olfaction (see **Figure 1.3.** and Introduction in Section 1, Chapter 2) [12].

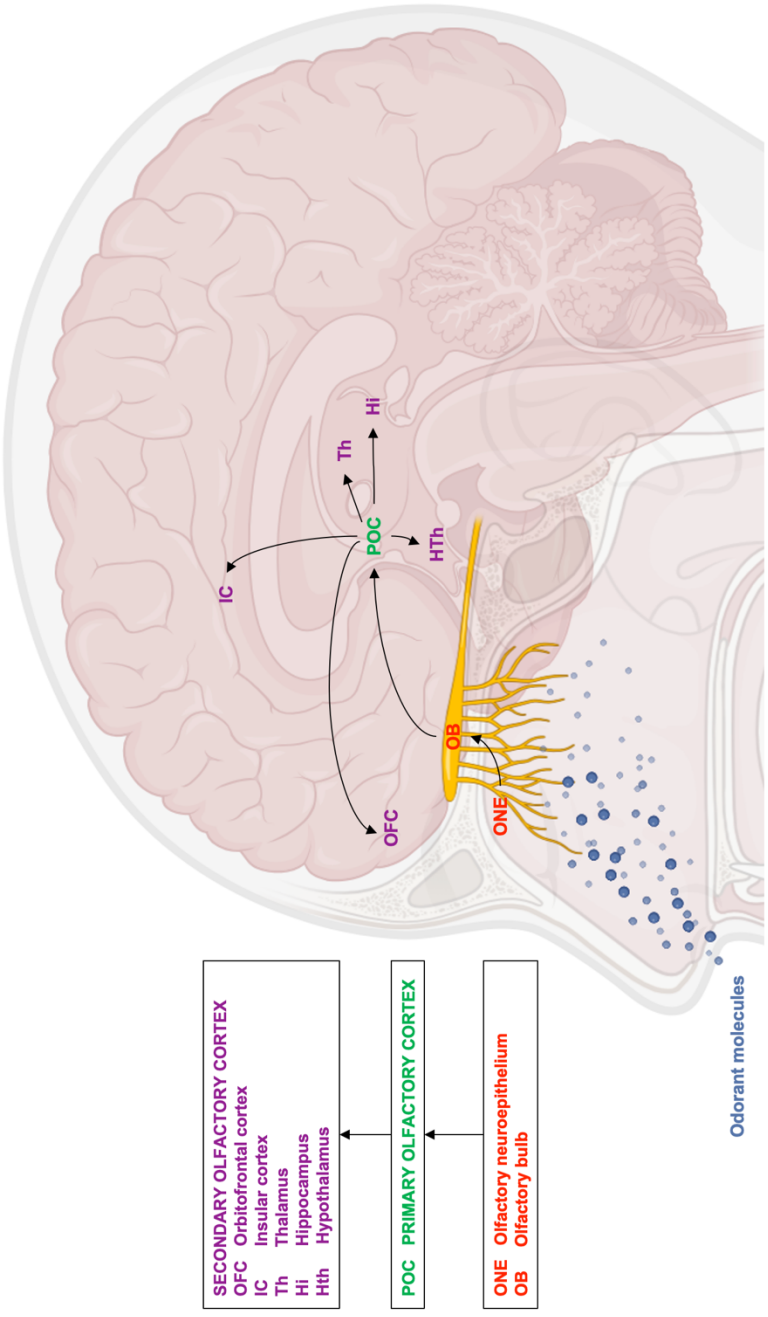

Figure 1.2. Olfactory cerebral pathways.

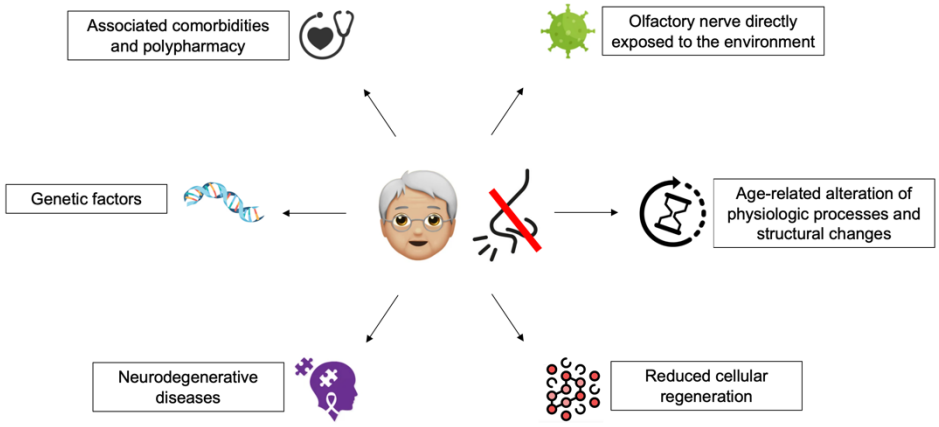

Figure 1.3. Etiologies of age-related olfactory decline.

How frequent is the problem? Olfactory impairment affects 1 out of 5 adults in the general population [3][13]. Fortunately, complete loss of smell is less frequent but would still hit approximately 5% of adults of all ages [11]. As previously mentioned, the prevalence of olfactory dysfunction increases massively with age since more than 50% of the population between 65 and 80 years old suffers from it, rising to 75% above 80 years old [14].

Olfactory function testing

"*How well can you smell odors?"* This simple question may bring some answers, but subjective assessment is far from entirely reliable, results from subjective and (semi-)objective testing methods being uncorrelated [15][16]. In this large study interrogating 6049 participants, almost 30% of the anosmic subjects (psychophysically tested afterward) would state their ability to smell as "average"[16]. In a cohort of patients with self-reported normal olfaction, the actual prevalence of anosmia increased significantly with age, representing 6.9% of the 61-70 year-old and 58% of the 80+ year-old subjects [17].

Psychophysical testing appears, therefore, mandatory to reliably assess olfactory function, especially in older adults.

Aside from electrophysiological testing and imaging techniques, psychophysical testing is the most accessible and commonly used semi-objective method to assess smell. Several tests have been developed and validated, including, among others, the Sniffin' Sticks test, the University of Pennsylvania Smell Identification Test (UPSIT), the San Diego Odor Identification Test (SDOIT), and the Scandinavian Odour-Identification Test (SOIT) [18]. Screening tests also exist, allowing for a very rapid – usually less than 5 minutes – evaluation of smell.

The Sniffin' Sticks extended test was developed and validated for routine clinical assessment of olfactory performance in 1997 by Thomas Hummel and colleagues [19]. This test is widely used in daily clinical practice in European countries. It has the advantage of covering the three subsets of olfactory testing: identification, threshold, and discrimination (see **Figure 1.4.**). The Sniffin' Sticks consist of pen-like odor dispensing devices placed approximately 2cm in front of the nostrils (for a detailed review of the methodology, see Rumeau et al. [20]).

The first module of the test aims to evaluate the olfactory threshold (T), i.e., the weakest concentration of an odor that a subject can perceive. The test comprises 16 triplets of pens, numbered from 1 to 16. Each triplet contains one pen impregnated with N-butanol, in progressively decreasing concentrations from pen number 1 to 16, and two other non-odorant pens. The subject must recognize the odorant pen between the three pens of a triplet. The odor threshold is determined using an ascending staircase procedure, starting with the strongest odor concentration. The second subset assesses one's ability to differentiate between two odors, named odor discrimination (D). This module also includes 16 triplets of pens. This time, two pens are impregnated with the same odor, and the third pen contains a different odor. The subject is asked to identify the pen impregnated with a distinct odor from the two other pens. The third module tests a subject's odor identification (I) performance. This test

consists of 16 pens, each containing a given odor. The subject must make a forced choice from a list of four descriptors each. (See **Table 1.1.** showing the 16 different odor items and their descriptors in the French-speaking version). The three modules are scored on 16 points and may be added up to obtain a global TDI olfactory score of 48 points.

Figure 1.4. The Sniffin' Sticks extended test.

Initially, a TDI score of < 16.5 was considered anosmia, a TDI score of ≥ 16.5 and ≤ 30.5 as hyposmia, and a TDI score of > 30.5 was defined as normosmia [20][21][22]. However, not only does olfactory function decline with age but it is also influenced by gender. Indeed, women usually tend to outperform men at smell testing [23]. Normative data have thus been established on large samples – and recently updated – which allow the classification of a subject's TDI score according to percentiles for age and gender [21][24]. The 10^{th} percentile may be used as a limit to separate normosmia from impaired olfaction. For example, the 10^{th} percentile odor identification score for a 78-year-old man is 7 compared to 12 for a 34-year-old woman.

Stick #				
1	**Orange**	Fraise	Mûre	Ananas
2	Fumée	**Cuir**	Colle	Herbe
3	Miel	Chocolat	Vanille	**Cannelle**
4	Ciboulette	Sapin	**Menthe**	Oignon
5	Noix de coco	Noix	**Banane**	Cerise
6	Pêche	**Citron**	Pomme	Pamplemousse
7	**Réglisse**	Menthe verte	Cerise	Biscuit
8	Moutarde	Menthol	Caoutchouc	**Térébenthine**
9	Oignon	**Ail**	Choucroute	Carotte
10	Cigarette	Vin	**Café**	Fumée
11	Melon	Orange	Pêche	**Pomme**
12	**Girofle**	Cannelle	Poivre	Moutarde
13	Poire	Pêche	Prune	**Ananas**
14	Camomille	**Rose**	Framboise	Cerise
15	**Anis**	Miel	Rhum	Sapin
16	Pain	**Poisson**	Fromage	Jambon

Table 1.1. List of the 16 odor items and their descriptors, in french, of the Sniffin' Sticks odor identification subtest.

The Sniffin' Sticks 12-item identification test is a shorter version originating from the extended test. Hummel and colleagues created this screening test to shorten the time taken to administer olfactory testing [25]. Indeed, 20 to 30 minutes are usually required to complete the Sniffin' Sticks three subsets. This short version consists of an identification test using 12 odors instead of 16 and takes only 4 minutes. According to the data from their sample, the authors proposed the

following classification: anosmia for a score of ≤ 6, hyposmia between 7 and 10, and normosmia when scoring 11 or 12 [25].

Chapter 3. Mechanisms linking olfactory impairment anf risk of mortality

Victoria Van Regemorter[1,2]*, Thomas Hummel[3], Flora Rosenzweig[4], André Mouraux[2], Philippe Rombaux[2,4], Caroline Huart[2,4]

[1]Department of Anesthesiology, Cliniques universitaires Saint-Luc, Brussels, Belgium; [2]Institute of Neuroscience, Université catholique de Louvain, Brussels, Belgium; [3]Smell and Taste Clinic, Department of Otorhinolaryngology, Dresden, Germany; [4]Department of Otorhinolaryngology, Cliniques universitaires Saint-Luc, Brussels, Belgium

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ABSTRACT

Olfaction is a sense involved in a complex set of tasks, influencing eating behavior, increasing awareness of environmental hazards and affecting social communication. Surprisingly, smell disorders are very frequent, especially in the elderly population.

Several recent studies conducted mostly in older subjects have demonstrated a strong association between olfactory impairment and overall mortality risk, with anosmia being even more predictive of 5-years mortality risk than cardiovascular disease. Presently, the underlying pathophysiology linking olfactory impairment to mortality remains unknown and only putative mechanisms are suggested.

This review aims to examine the link between olfactory impairment and mortality and to discuss existing ideas on underlying existing mechanisms including, (1) the effect of olfactory loss on nutrition, life-threatening situations and social interactions, (2) associated neurodegenerative diseases, (3) accelerated brain aging and (4) reflection of general health status being reflected in olfactory function.

INTRODUCTION

Olfactory impairment (OI) is known to occur during the process of aging (odds ratio [OR] = 1.55 for every 5-year increase in age) [26]. It is estimated that more than 50% of the population aged between 65 and 80 years old exhibit OI, increasing to 75% above 80 years old [27]. Several hypotheses are proposed to explain this age-related decline of olfaction.

First, the olfactory nerve, originating from the nasal fossa, is the only cranial nerve directly exposed to the environment, which makes it vulnerable to exposure to toxins, infection, trauma, and airborne pollutants [6][8][28][29].

Second, age-related alteration of physiological processes and structural changes within the nose, olfactory epithelium, olfactory bulb and higher brain regions seem to contribute greatly to this deterioration [14][27][30][31][32][33].

Third, brain aging or environmental exposure could reduce the cellular regeneration found at the different levels of the olfactory system [34].

Fourth, genetic factors could also be involved. For example, it has been shown that carriers of val/val genotype of the brain-derived neurotrophic factor (BDNF) val66met polymorphism present a marked aging-associated decline in olfactory function [35]. Apolipoprotein E (ApoE) ε4 allele carriers seem to experience greater olfactory decline than the non-carriers [36]. ApoE may also contribute to neuronal regenerative processes and to the development of neurodegenerative diseases. Interestingly, the combination of ApoE ε4 allele and OI in a non-demented elderly population predicts a larger decline in global cognitive function [37][38]. As for cognitively impaired individuals, ApoE ε4 allele carriers also show a more significant decline in cognitive abilities as well as in odor identification [36]. However, a twin study suggests low heritability coefficients regarding olfactory function [39].

Fifth, age-related OI could reflect early involvement of olfactory-related brain areas by the neuropathological processes associated with neurodegenerative diseases, such as Alzheimer's disease (AD) and Parkinson's disease (PD). Even if the exact mechanisms underlying OI in AD and PD are not completely understood, olfactory brain structures are affected early in their courses [33][40] and OI precedes clinical diagnosis. Regarding AD, OI may already be present in patients with mild cognitive impairment (MCI, cognitive dysfunction exceeding normal "age-related" decline, yet not meeting the criteria for dementia) [41]. It is known that approximately 70% of MCI patients will ultimately convert to AD [42]. Yet, recent data converge towards the idea that olfactory-impaired MCI patients are more prone to develop AD than those without OI [43][44][45][46]. Overall, these findings make OI a potential early predictor for AD development. PD is also marked by early OI, which typically precedes motor symptoms by at least 5 years and thus can be used as a biomarker for the diagnosis of PD [33][47][48]. Moreover, a 7-year prospective study conducted in newly diagnosed PD patients reported that hyposmia at diagnosis of PD is associated with further development of cognitive deficits, making OI a predictor of dementia in this setting [49].

Sixth, OI has been shown to accompany a variety of diseases. In addition to the link to neurodegenerative diseases, OI has been reported to occur in schizophrenia, epilepsy, systemic and endocrine diseases (e.g. hypothyroidism, type 2 diabetes mellitus), chronic kidney or liver failure [11][50][51]. Of note, a recent study involving type 2 diabetic patients demonstrated not only increased OI in this population compared to controls but also diminished abilities in specific cognitive tests. Besides, once again, they found a strong association between OI and specific memory impairment in this population [52]. As for smoking, which is known to interfere with olfactory performance, the effect is equivocal or weak and mostly seen in long-standing heavy smokers [53]. Alcohol's abuse negative effects on olfaction could be related to alterations in brain areas involved in olfactory processing [26]. Higher probability of comorbidities with age comes

along with the associated polypharmacy. Despite little evidence-based data, it is commonly thought that medication may affect taste and smell functions [11]. Drugs are thought to interact with many different molecular targets of the olfactory pathway from the olfactory receptors to central processes [54][55][56]. A long list of medications might be involved in smell loss, including antibiotics, antidepressant and antipsychotic drugs, antihypertensive drugs (e.g. calcium channel blockers), opioids, sildenafil [11][57]. However, it is difficult to distinguish drug-induced OI from the effect of the underlying medical issue for which the drug is taken. Landis et al. did not find a correlation between olfactory function and the number of drugs taken [50]. Nevertheless, a recent study showed a significant correlation between the number of drugs taken and both worse olfactory threshold function and, interestingly, worse MMSE scores [58]. The authors justified this finding by the fact that these parameters are usually age-related. However, they did not control for comorbidities, which in fact could have explained in part these results.

SUMMARY OF EXISTING STUDIES LINKING OLFACTORY IMPAIRMENT AND MORTALITY

Until now, seven longitudinal studies have been published on the relationship between olfactory function at baseline and risk of mortality [59][60][61][62][63][64][65]. Demographics and methods are summarized in **Table 1.2**. Statistics and main results are summarized in **Table 1.3.** We deliberately decided to include only studies with psychophysical assessment of olfactory function using well-known validated identification tests since self-assessment of olfactory function is not reliable [15][17][16][66]. Together, these studies included a total of 13,366 individuals, male and female, aged 40 and older, with older people representing the majority. In regard to age groups, results vary between studies. Some found a stronger OI-mortality link in older subjects, while others demonstrated a slightly stronger relationship in middle-aged groups [60][64][65]. This latter finding may be due to the increased

prevalence of anosmia with advancing age. Length of follow-up varied according to studies, mainly ranging from 4-5 years up to 10-13 years. Exclusion criteria, mostly including dementia or neurologic diseases, were found in four studies and are discussed below.

These studies cannot be directly compared due to methodological differences. However, all yield similar results. Regardless of the statistical method used, the relationship between OI and mortality risk was statistically significant and strong. In addition, the association was found to be dose-dependent, meaning anosmic people have a greater risk of death than hyposmic people.

Unfortunately, while clearly revealing the existence of a link between OI and risk of mortality, these studies leave possible explanations of such a link quite unexplored. Indeed, cause-specific mortality is only explored in one study [65] whereas others do not report cause of death. Yet, this parameter could have largely contributed to the understanding of the mechanisms of the OI-mortality relationship. Nevertheless, a large number of covariates were controlled, which certainly adds more data to progress through the current hypotheses. Though being a key feature, the causal involvement of neurodegenerative diseases is still left quite unanswered in these studies.

TABLE 1 | Studies linking olfactory impairment and mortality – Demographic data and methods.

References	Sample size (n)	Length of follow-up	Mean age, age range	Exclusion criteria	Olfactory test
Wilson et al., 2011	1162	Mean of 4.2 years, range: 0–9	79.7 years, no data	Diagnosis of dementia or PD	Brief Smell Identification Test (BSIT) (12 points score)
Gopinath et al., 2012	1636	5 years	Presence of OI: 77.2 years, no data Absence of OI: 72.1 years, no data	None	San Diego Odor Identification Test (SDOIT) (8 points score)
Pinto et al., 2014	2918	5 years	68 years, 57–85	None	Validated modified score using items from the Sniffin' Sticks identification test (5 points score)
Devanand et al., 2015	1169	Mean of 4.1 years, range 0–9.8	80.4 years, ≥65	Clinical stroke, PD, atypical Parkinsonian syndrome diagnoses, schizophrenia, and other psychotic disorders	University of Pennsylvania Smell Identification Test (UPSIT) (40 points score)
Schubert et al., 2016	2418	Mean of 12.8 years, maximum 17 years	69 years, 53–97	None	San Diego Odor Identification Test (SDOIT) (8 points score)
Ekström et al., 2017	1774	10 years	63.5 years, 40–90	Individuals who met criteria for dementia	Modified version of the Scandinavian Odor-Identification test (SOIT) (13 points score)
Liu et al., 2019	2289	13 years	75.6 years, 71–82	Difficulty in walking a quarter mile, climbing 10 steps or performing activities of daily living, active cancer treatment in the previous 3 years	Brief Smell Identification Test (BSIT) (12 points score)

PD, Parkinson's disease; OI, olfactory impairment.

Table 1.2. Studies linking olfactory impairment and mortality – Demographic data and methods.

TABLE 2 | Studies linking olfactory impairment and mortality – Statistics and results.

References	Statistical analyses	Covariates	Main results (according to adjustment for covariates)
Wilson et al., 2011	Cox proportional hazard models	Age, sex, education	HR = 0.94 (95%CI: 0.90, 0.98)	HR predicting mortality for each additional correct answer on the BSIT score.
		Boston Naming Test	HR = 0.94 (95%CI: 0.90, 0.99)	
		Katz scale, cardiovascular risk factors and conditions	HR = 0.95 (95%CI: 0.90, 0.99)	
		Cognitive, social and physical activity, depressive symptoms	HR = 0.95 (95%CI: 0.91, 0.99)	
Gopinath et al., 2012	Cox proportional hazard models – Multivariate logistic regression	Age, sex	HR = 1.99 (95%CI: 1.42, 2.80)	HR predicting mortality for moderate OI (SDOIT ≤ 3).
		BMI, systolic blood pressure, current smoking status, alcohol consumption, poor self-rated health, visual impairment, hypertension, diabetes, history of cancer, angina, stroke, acute myocardial infarction	HR = 2.04 (95%CI: 1.41, 2.95)	
		Serum total cholesterol	HR = 1.68 (95%CI: 1.10, 2.56)	
		Cognitive impairment	HR = 1.51 (95%CI: 0.96, 2.38)	
Pinto et al., 2014	Multivariate logistic regression	None	OR = 5.85 (95%CI: 3.76, 9.10)	OR predicting mortality for anosmic subjects (4–5 errors on the Sniffin' Sticks modified score) compared to controls.
		Age, sex, education	OR = 3.24 (95%CI: 1.99, 5.28)	
		Age, sex, education, comorbidity index	OR = 3.41 (95%CI: 2.06, 5.64)	
		Age, sex, education, cardiovascular diseases, cancer, lung disease, stroke, diabetes, liver damage	OR = 3.37 (95%CI: 2.04, 5.57)	

Table 1.3. Studies linking olfactory impairment and mortality – Statistics and results.

TABLE 2 | Continued

Devanand et al., 2015	Cox proportional hazard models – Multivariate logistic regression	None		HR = 1.068 (95%CI: 1.053, 1.083)	HR predicting mortality for each additional error on the UPSIT score.
		Age, education, race/ethnicity, gender, spanish language, comorbidity index, dementia, depression, head injury, alcohol abuse, BMI, smoking, hearing/vision impairment		HR = 1.049 (95%CI: 1.030, 1.068)	
Schubert et al., 2016	Cox proportional hazard models – Multivariate logistic regression	Age, sex		HR = 1.46 (95%CI: 1.24, 1.73)	HR predicting mortality for OI (SDOIT ≤ 6).
		Age, sex, education, hypertension, diabetes, cardiovascular disease, cancer, cognitive impairment, frailty, smoking, exercise, BMI, alcohol		HR = 1.29 (95%CI: 1.08, 1.54)	
		Age, sex, education, hypertension, diabetes, cardiovascular disease, cancer, cognitive impairment, frailty, smoking, exercise, BMI, alcohol, IMT, CRP, IL-6		HR = 1.28 (95%CI: 1.07, 1.52)	
Ekström et al., 2017	Cox proportional hazard models – Multivariate logistic regression	None		HR = 0.74 (95%CI: 0.71, 0.77)	HR predicting mortality for each additional correct answer on the SOIT.
		Age, sex		HR = 0.91 (95%CI: 0.87, 0.95)	
		Years of education		HR = 0.91 (95%CI: 0.87, 0.96)	
		Health variables		HR = 0.91 (95%CI: 0.87, 0.97)	
		Cognitive performance		HR = 0.92 (95%CI: 0.87, 0.97)	
		Dementia conversion		HR = 0.92 (95%CI: 0.88, 0.97)	
		Apolipoprotein E ε4		HR = 0.92 (95%CI: 0.87, 0.97)	

Table 1.3. Studies linking olfactory impairment and mortality – Statistics and results (Continued).

TABLE 2 | Continued

Liu et al., 2019	Mediation analyses using risk ratio scale	Age, sex, race, education, BMI, drinking, brisk walking, smoking, self-reported general health status, cardiovascular disease, cancer, diabetes, hypertension, depressive symptoms, chronic kidney disease	RR = 1.46 (95%CI: 1.27, 1.67)	RR predicting mortality for OI (BSIT ≤ 8).

HR, hazard ratio; CI, confidence interval; BMI, body mass index; BSIT, Brief Smell Identification Test; OI, olfactory impairment; SDOIT, San Diego Odor Identification Test; OR, odds ratio; UPSIT, University of Pennsylvania Smell Identification Test; IMT, carotid intima plus media thickness; CRP, C-reactive protein; IL-6, interleukin-6; SOIT, Scandinavian Odor-Identification Test; RR, risk ratio.

Table 1.3. Studies linking olfactory impairment and mortality – Statistics and results (Continued).

POSSIBLE MECHANISMS LINKING OLFACTORY IMPAIRMENT AND RISK OF MORTALITY

At the moment, the underlying physiopathology linking olfactory impairment to mortality remains unknown. Based on existing evidence and on data from the mortality studies, we will present an overview of current hypotheses.

(1) Effects of olfactory loss on eating behavior, danger warning and social interaction

Olfaction is known to play a role in eating behavior, danger warning and social interaction [2]. OI will therefore have various consequences on these three human functions, which might directly or indirectly lead to decreased health.

First, malnutrition may be a direct consequence of OI as taste and smell are intrinsically linked. In fact, OI may lead to a decreased ability to enjoy food, decreased appetite and food intake, as well as change in body weight and increased risk for chronic disease. People suffering from OI might either maintain their weight, or eat less, or on the contrary eat more since food would become tasteless; reasons for this remain unclear [3]. Interestingly, there is growing evidence that the olfactory system could greatly contribute in the regulation of food intake and energy balance, through its effect on sympathetic and parasympathetic tone [67][68][69]. Indeed, receptors to a variety of orexigenic and anorexigenic molecules (i.e. insulin, leptin, ghrelin, neuropeptide Y, nutrient glucose) were found in the olfactory epithelium and in the olfactory bulb [67][70]. It was shown that older women with OI had poorer diet quality over 5 years [71] and that a population of older U.S. female and male adults displayed low body mass index (BMI) [72]. Still, there remain controversies in the literature regarding the association between malnutrition and OI in geriatric patients [32]. Similarly, the relationship between OI and obesity yield contradictory results, some studies demonstrating a correlation (mainly through increased threshold detection of odors [67][73], while others did not [74]. Some authors suggest that the wide

range of both etiologies and endocrinologic consequences of obesity could explain these conflicting findings [67]. Among our seven reviewed studies, only a few measured BMI of the subjects. One study found that OI was associated with decreased BMI [60]. The other showed that subjects who did not enjoy eating or had a low BMI had increased mortality, whereas those who had a high BMI had decreased mortality [61]. Weight loss, as a surrogate marker for malnutrition, was also found to contribute to the association between OI and mortality [65]. Indeed, their mediation analysis demonstrated that weight loss could account for respectively 6% and 11% of the 10-year and 13-year higher mortality linked to poor olfaction.

OI might also increase risk of death as a result of not smelling danger signals in the household environment. A U.S. survey showed that respectively 20.3% and 31.3% of adults older than 70 years were not able to identify the warning odors of smoke and natural gas [75]. OI thus exposes to risks associated with cooking accidents, fires or gas leaks and ingestion of spoiled foods or toxic substances [76]. Anosmic people experience hazardous events 2 to 3 times more often than normosmic subjects [77]. Although the 7 studies did not take these events into consideration for analysis of cause-specific mortality, death rate from unintentional poisoning or fire (not necessarily related to OI) is actually low (1.7-4.7 per 100,000) [78].

Olfactory function is known to influence quality of life. Notably, people with OI typically suffer from depressive symptoms [3][79][80][81]. One proposed explanation is that dysfunction or absence of olfactory bulb might result in the dysfunction of various cellular processes and pathways within the hippocampus [82]. Some of the mortality studies reported that the subjects who died showed more depressive signs [59][64]. However, the association of OI with mortality persisted after controlling for depressive symptoms [59]. OI is associated with reduced social network size [83], and recent work showed that reduced in-

person physical contact with others might partially mediate the link between OI and mortality in females [84].

(2) Associated neurodegenerative diseases

At present, OI has become a well-known early biomarker for a broad spectrum of neurodegenerative diseases. Therefore, it is not surprising that neurodegenerative diseases have been investigated as a possible mediator in the relationship between OI and mortality. Despite some conflicting results, evidence is progressively increasing that neurodegenerative diseases might partly explain this relationship.

The majority of the reviewed studies included cognitive function at baseline as a covariate. In three studies, controlling for cognitive performance at baseline did not change the results. Nevertheless, Wilson et al. excluded patients with a diagnosis of dementia or PD at baseline and used a measure of cognitive activity frequency in leisure time, which seems to weakly reflect cognitive function [59]. Schubert et al. did not adjust the results exclusively for cognitive function but rather included additional covariates for adjustment, so that the precise impact of cognitive function remains unknown [63]. In addition, Ekström et al. also specifically addressed the question of dementia conversion and found that the OI-mortality relationship was independent from it [64]. On the contrary, three other studies did show a potential mediator effect of cognitive function on mortality [61][62][65]. Two found that the association between OI and mortality was lowered when controlling for dementia, yet remained statistically significant. Of note, OI was shown to be associated with future cognitive decline in cognitively intact subjects [44]. Moreover, there is evidence of existing postmortem markers of neurodegenerative disease in the brain of subjects without previous clinical signs of MCI or AD [85]. Therefore, one hypothetical explanation for the absence or weak mediating effect of cognitive function on mortality might be that olfaction is altered while clinical cognitive function is not

yet affected and thus undiagnosed. Only Gopinath et al. came to a non-significant association between OI and mortality risk after adjustment for cognitive impairment [60]. This would suggest a mediating role of cognitive function, although the authors clearly state this finding could be due to weak statistical power. More interestingly, the only analysis of cause-specific mortality showed that the strongest causal association found was between OI and death associated with dementia or PD [65]. Indeed, their mediation analysis showed that dementia or PD could account for 22% of the higher 10-year mortality linked to poor olfaction. Lastly, Devanand et al. questions the fact that neurodegenerative disorders lead to excess mortality. However, recent evidence suggests otherwise [62]. In 2014, AD was the sixth leading cause of death in the U.S., representing 3.6% of total mortality with an age-adjusted death rate of 25.4 per 100,000 citizens [86]. As for PD, a meta-analysis showed a pooled mortality ratio of approximately 1.5 compared to controls [87]. Also, mean duration until death varies from 6.9 to 14.3 years. This might also partially explain why dementia conversion does not seem to mediate the OI-mortality link despite a 10-year follow-up [64], since death associated with PD may occur after more than 10 years. PD-related mortality was shown to be significantly increased by the presence of MCI at baseline [88]. This finding supports the idea of a correlation between OI, PD and mortality risk.

Finally, adjusting for ApoE ε4 genotype, associated with cognitive decline and OI [36], did not attenuate the association between OI and mortality [62][64].

In conclusion, even if available data remain controversial, there seems to be growing evidence that neurodegenerative diseases, through cognitive dysfunction, may be a potential mediator in the relationship connecting OI to mortality risk.

(3) Accelerated brain aging

One of the special features of the olfactory system is its extraordinary plasticity and continuing neurogenesis through adulthood, at least at the level of the olfactory epithelium (for recent review see Huart et al. [34]). Mechanisms underlying these neural abilities have been largely investigated mainly in rodents; indeed, the paucity of human data remains controversial. Adult neurogenesis is thought to occur both peripherally and centrally, in three different locations. First, proliferating stem cells, located within the olfactory epithelium differentiate into olfactory receptor neurons. Secondly, neural stem cells coming from the walls of the lateral ventricle could migrate following the rostral migratory stream towards the olfactory bulb (OB) to give rise to olfactory interneurons [89]. Thirdly, some animal data suggest the presence of progenitor cells lying directly within the OB [34]. For now, however, all this remains somewhat hypothetical in adult human brains. Yet, clinical findings support the idea of high plasticity of the olfactory system. For instance, it is widely acknowledged that the OB is subject to significant volume changes, as a function of olfactory performance. Indeed, OI is associated with reduced OB volume, while recovery of olfactory function correlates with OB volume [90][91][92][93][94]. These volume fluctuations probably depend on bottom-up [95] and top-down processes [96]. In addition, structural brain modifications could also occur beyond the OB [97]. Finally, olfactory plasticity has also been recently highlighted by olfactory training, which was found to improve significantly olfactory skills regardless of baseline olfactory function [98] and to lead to increased cortical thickness of certain brain areas [99]. Interestingly, olfactory training was also shown to improve verbal function and subjective well-being in older people [100].

Importantly, vision and hearing impairment were not associated with mortality nor did they alter the OI-mortality relationship, suggesting that death could not be explained by sensory loss more broadly [62][63]. Still, some previous studies have shown a possible link between vision and/or hearing impairment and

mortality, evidence for the impact of vision impairment alone remaining weaker [63][101][102]. It is also important to underline the fact that all humans do not age equally. That is why physiological age might be more relevant than the chronological age. It may be hypothesized that decline in olfactory function could indicate a more advanced physiological age. Indeed, it was found that idiopathic age-related decline in olfactory function was much smaller in the healthy, non-medicated, non-smoking population [53]. On the contrary, it was shown that taste and smell disorders were associated with an increased risk of frailty in the older population [103][104]. Among the mortality studies, controlling for performance in activities of daily living or frailty score did not attenuate the effect [61][63]. Global sensory impairment (including the five classical senses: smell, taste, hearing, vision and touch) predicts 5-year mortality, but also major components of physical frailty (e.g. slow gait, weight loss, low activity) [105]. The same authors developed the concept that multisensory loss of function could reflect a common underlying aging process [106].

To summarize, we hypothesize that OI reflects a decline in brain plasticity, and could be seen more globally as an indicator of lowered physiologic repair function. This could explain, at least partly, the pathway toward increased mortality. Brain aging could make the olfactory system as well as other brain structures more vulnerable and less capable of recovering from insults. This highlights the current need to think in terms of physiological age and frailty status. Whether frailty mediates the relationship between OI and mortality still requires more evidence.

(4) Reflection of general poor health

OI is known to be associated with a wide range of illnesses and is thought to be a marker of poor health. Landis et al. showed a negative correlation between olfactory function and the number of comorbid conditions [50]. Self-reported poor health status was associated with OI in one study [65]. However, the association

between OI and mortality risk was mostly driven by the subjects with baseline excellent to good health, which might question the idea of OI being merely a marker of poor health. The authors hypothesized either that OI in healthy older people might hide an underneath life-threatening condition or that the cumulative effect of multiple comorbid conditions might outweigh the effect of OI on death. Moreover, half of the analyzed studies adjusted their results for comorbid conditions, with either little or no effect on the OI-mortality link [61][62][63][64]. Controlling for smoking or alcohol abuse did not attenuate the link between OI and mortality [61][62]. Some authors also suggested that high levels of inflammatory markers (interleukin-6, C-reactive protein) could be associated with frailty, atherosclerosis and also with OI [107][108][109]. However, adjusting for these variables did not attenuate the link between OI and mortality [63]. Hence, whether OI is a marker of poor health remains doubtful. The only assertion that can be made is that OI is a strong and independent risk factor for death, regardless of health status.

Since controlling for comorbid conditions had little or no effect on the OI-mortality link, this would then suggest a weak impact of cardiovascular diseases or metabolic disorders (being part of the comorbidity indexes used in the studies).

However, analysis of cause-specific mortality revealed that OI was modestly associated with death from cardiovascular disease, but not from cancer or respiratory diseases [65]. Furthermore, the association between OI and mortality did not remain significant after adjusting for total serum cholesterol, though potentially explained by reduced statistical power [60]. Physical exercise and use of statins were found to decrease the incidence of OI [108]. Indeed, both are known to improve cardiovascular health and to lower the risk of atherosclerosis, which is the main hallmark of cardiovascular diseases. Additionally, statins may also directly provide to the brain (and thereby to the olfactory system) their positive pleiotropic effects on endothelial function, oxidative stress and vascular inflammation. This would be consistent with the reduced risk of OI being specific

to statins crossing well the blood-brain barrier in the study from Schubert et al. [108]. However, in a mouse model, administration of atorvastatin (classified as not crossing the blood-brain barrier) could still enhance the recovery of olfactory function, likely through the promotion of cellular proliferation and neural regeneration of the olfactory epithelium [110][111]. Carotid artery intima media thickness (IMT), a biomarker of generalized atherosclerosis, was shown to be associated with a decline in odor identification performance at 5 years, but only before 60 years old [112][113]. Nevertheless, the association between OI and mortality remained statistically significant after adjusting for IMT [63]. Also, OI could be associated to the intake of antihypertensive drugs [57]. Therefore, cardiovascular diseases might be somehow connected to OI. Yet, evidence remains sparse and further studies are needed.

Obesity, insulin resistance and type 2 diabetes mellitus constitute a well-known continuum which represents a major burden in terms of public health and mortality. In rodent obesity models, the olfactory bulb developed insulin resistance which could then be responsible for the disruption of olfactory function [67]. Human data also support the fact that insulin resistance could affect negatively olfactory function. Indeed, a recent study found that older adults with high insulin resistance (quantified by the HOMA-IR test) had an approximately two-fold increased odds of OI compared with subjects with low insulin resistance [70]. This could explain, at least in part, the independent association found between type 2 diabetes mellitus (in which insulin resistance represents the key mechanism) and OI [52][60][74]. OI in type 2 diabetes mellitus might also be due to microvascular injury since OI was mainly found in diabetic patients already suffering from the microvascular complications of this disease [74]. Regarding mortality studies, diabetes mellitus was associated with OI in one study [60] but was not in another one more recent [65]. Three studies included diabetes mellitus in their controlled variables, but the correlation between OI and mortality remained unchanged, thus also suggesting a weak impact of diabetes mellitus.

Regarding the link of obesity, insulin resistance and type 2 diabetes mellitus with OI, controversies thus persist on many points.

Finally, due to its direct contact to the outside, the olfactory system may be an easy target for environmental insults. Indeed, olfaction is altered by air pollutants and by exposure to a variety of toxic agents (e.g. metallic compounds) [28][29][114]. The airborne toxicants may also make their way to the brain directly through the olfactory pathway, leading to neuronal damage. Of note, it was shown that high levels of air pollution could result in neurodegenerative diseases-related pathology within the olfactory bulb [115]. Pollution and toxic exposure have been linked to poor health and might thus constitute a potential mediator in the relationship between OI and mortality [116].

CONCLUSION

Studies agree that OI is an indicator of increased mortality risk in the older population. Several hypothetical mechanisms are suggested, yet the extent to which they contribute to this association remains an open question. To our opinion, the effects of olfactory impairment on eating behavior, danger warning and social interaction do exist, although their importance in this context seems minor. Olfactory impairment and poor health status seem to be linked in some ways, though the exact relationship remains poorly understood. On the contrary, based on current evidence, neurodegenerative diseases and advanced physiological brain aging appear to us as the most likely involved. The olfactory system plays a determinant role and further attention should be given to these potential mechanisms underlying the robust OI-mortality association. In the future, we should also address the question whether the recovery of olfactory function could have beneficial effects on outcome.

Chapter 4. Frailty in the perioperative setting

Introduction

Surgery plays a key role in healthcare. Indeed, surgical volume is nowadays massive since about more than 300 million surgical procedures are annually required to address the needs of the global population [117]. And while lack of universal access to surgical care is responsible for an estimated 16.2 million deaths annually from conditions needing surgery [118], surgical care also paradoxically represents a major source of morbidity and mortality. It was suggested that 4.2 million people worldwide would die within 30 days of surgery each year, ranking third among causes of mortality after ischemic heart disease and stroke [119]. Overall, we may estimate that postoperative complications occur in up to 20% of the patients, and short-term mortality declares in about 1 to 4% [120].

Besides, the rising average age of the population comes along with higher surgery rates and thereby with an increased risk of morbidity and mortality in the perioperative period. Morbidity after surgery in elderly patients includes postoperative surgery-related complications, but also geriatric syndrome (including cognitive decline) and post-discharge institutionalization [121]. Interestingly, in-hospital surgery-related mortality is known to be correlated with age as it was found to represent 1.2% of patients aged 65-74, 2,3% when aged 75-84 and 5.6% when aged 85-94 [122].

Indeed, surgery and anesthesia act together as a heavy inflammatory stressor on the human body. Throughout this period, the patient must draw on their physiological reserve to shift from homeostasis – a self-regulating process maintaining internal stability while adjusting to changing external conditions – to allostasis – a general adaptative reaction to stress [123][124]. Therefore, when evaluating the risks in an older patient, it seems that physiological age rather

than chronological age would be more relevant to consider [125]. Setting aside age per se, only partially responsible for a rise in postoperative risk, the concept of frailty emerges from this lowered capacity of adapting. Frailty may be defined as a biological syndrome of decreased reserve and resistance to stressors, resulting from multiple physiologic systems and causing vulnerability to adverse outcomes [126].

Preoperative evaluation of frailty

Routine preoperative frailty assessment has progressively become recommended by many surgeons, geriatricians and anesthesiologists societies and guidelines, including notably the American Geriatrics Society and the American college of surgeons [127]. Currently, clinical factors determining frailty remain not entirely known or even understood. As a consequence, numerous frailty instruments coexist with no clear consensus regarding frailty assessment in the surgical context [128].

Among the multitude of tests available, the Fried Phenotype and the Frailty Index have both been largely used and studied tests, mostly by geriatricians [129][130]. Each one aims to evaluate a different model of frailty, respectively, the phenotype model and the cumulative deficit model. Fried Phenotype comprises the following components: unintentional weight loss, weakness at grip strength, self-reported exhaustion, slow gait speed, low physical activity level [129]. Whereas the Frailty Index's principle is to add up any "deficit in health" of a patient, which may correspond to symptoms, signs, diseases, disabilities, or biomarkers abnormalities [131].

In 2006, Rolfson et al validated a frailty screening tool consisting of a brief and user-friendly interview named the Edmonton Frail Scale (EFS) [132]. This test explores nine domains of frailty: cognition, general health status, functional independence, social support, medication use, nutrition, mood, continence, and

functional performance (see **Table 1.4.**, adapted from Rolfson et al. [132]). The EFS has been shown to be performant in frailty stratification and has the advantage of being quickly and reliably performed by non-geriatricians [133]. This test has thus been widely explored in the perioperative context.

Frailty domain	Item	0 point	1 point	2 points
Cognition	Please imagine that this pre-drawn circle is a clock. I would like you to place the numbers in the correct positions then place the hands to indicate a time of "ten after eleven"	No errors	Minor spacing errors	Other errors
General health status	In the past year, how many times have you been admitted to a hospital?	0	1-2	≥2
	In general, how would you describe your health?	'Excellent', 'Very good', 'Good'	'Fair'	'Poor'
Functional independence	With how many of the following activities do you require help? (meal preparation, shopping, transportation, telephone, housekeeping, laundry, managing money, taking medications)	0-1	2-4	5-8
Social support	When you need help, can you count on someone who is willing and able to meet your needs?	Always	Sometimes	Never
Medication use	Do you use five or more different prescription medications on a regular basis?	No	Yes	
	At times, do you forget to take your prescription medications?	No	Yes	
Nutrition	Have you recently lost weight such that your clothing has become looser?	No	Yes	
Mood	Do you often feel sad or depressed?	No	Yes	
Continence	Do you have a problem with losing control of urine when you don't want to?	No	Yes	
Functional performance	I would like you to sit in this chair with your back and arms resting. Then, when I say 'GO', please stand up and walk at a safe and comfortable pace to the mark on the floor (approximately 3 m away), return to the chair and sit down.	0-10 s	11-20 s	One of >20 s, patient unwilling, or requires assistance

Table 1.4. The Edmonton Frail Scale (adapted from Rolfson et al. [132]).

The Clinical Frailty Scale (CFS) has been developed as part of the Canadian Study of Health and Aging and was validated in 2005 [134]. This assessment tool aims to measure frailty based on clinical judgment. The examiner has to choose between 7 clinical categories ranging from "Very fit" (1 point) to "Severely frail" (7 points) (see **Figure 1.5.**, adapted from Rockwood et al. [134] and Rockwood and Theou [135]). The CFS is also characterized by its rapidity and may be readily administered in the perioperative setting. A recent study showed a relatively close agreement between anesthesiologists and geriatricians when using this test, particularly in non-frail and severely frail patients [136].

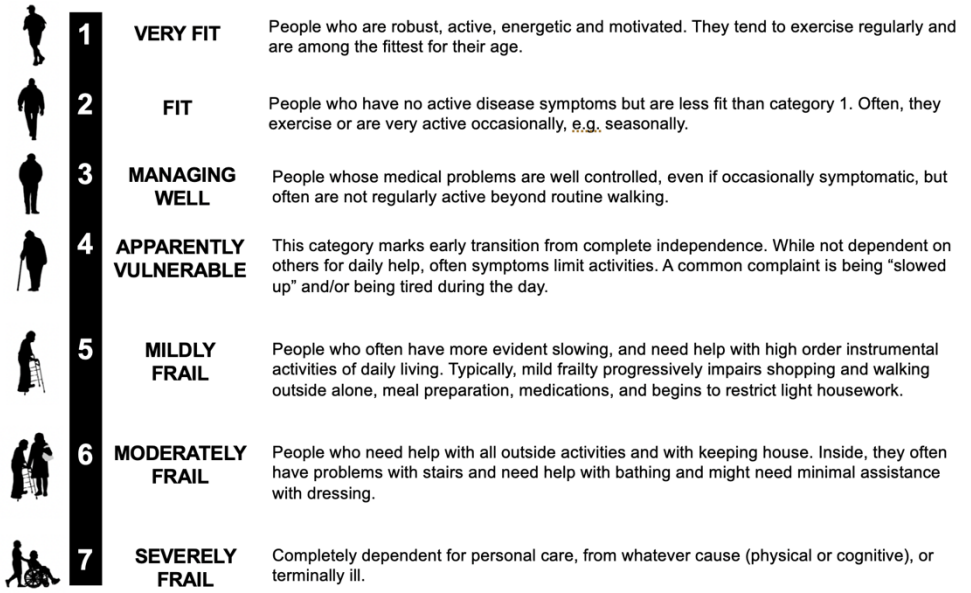

Figure 1.5. The Clinical Frailty Scale (adapted from Rockwood et al. [134] and Rockwood and Theou [135]).

Frailty and postoperative outcome

It is now well established that screening for frailty should be part of the preoperative assessment as a key component to predict risk in surgical adult patients. Indeed, frailty status has been shown to be an independent risk factor for 30-day, 90-day, 180-day and 1-year postoperative mortality [137][138]. Regarding the prediction of post-surgical mortality, the CFS seems to be the best to administer in a clinical setting. It had the largest effect size in a systematic review and meta-analysis of 70 studies, displaying a greater than 4.5-fold increase in the odds of death [128]. Besides, the CFS added significant predictive value to a risk prediction model with age, sex, American Society of Anesthesiologists (ASA) physical status and procedural risk, in a multicenter prospective cohort of elective noncardiac surgery patients ≥65 years old [139]. Of course, other frailty instruments were also proved to be predictive of

postoperative mortality. The EFS improved the prediction of 30-day mortality over the use of Euroscore II – a cardiac risk model for predicting mortality after cardiac surgery – in an older population undergoing cardiac surgery [140]. As to postoperative complications, the CFS was shown to be useful despite being dethroned by the EFS and the Fried Phenotype for that matter [128]. In any case, being frail was found to be associated to increased postoperative mortality, complications and length of stay, regardless of the type of frailty tool performed [137].

Evaluation of postoperative outcome

A poor outcome after surgery may be interpreted as any deviation from the normal postoperative course. This would gather medical and surgical postoperative complications. Of course, death is the worst possible outcome. To evaluate and classify these postoperative events, we used the Clavien-Dindo classification (**Table 1.5.,** adapted from Dindo et al. [141]). In our work, we did not regard grade 1 complications as meaningful events.

Of note, postoperative neurocognitive dysfunction is also considered a poor postsurgical outcome, from a cognitive point of view. Yet, it requires a particular assessment (see Section 1, Chapter 5).

Grade 1	Any deviation from the normal postoperative course without the need for pharmacological treatment, or surgical, endoscopic, and radiological interventions. *Allowed therapeutic regimens are drugs as antiemetics, antipyretics, analgesics, diuretics and electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside.*
Grade 2	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. *Blood transfusions and total parenteral nutrition are also included.*
Grade 3	Requiring surgical, endoscopic, or radiological intervention.
Grade 4	Life-threatening complications (*including central nervous system complications*) requiring IC/ICU management.
Grade 5	Death.

Table 1.5. Clavien-Dindo classification (adapted from Dindo et al. [141]).

Chapter 5. Perioperative cognitive function

Introduction

Aging does not spare the brain, obviously. The incidence of cognitive impairment in the US population was estimated at 60 cases per 1000 persons-year [142]. It makes thus sense that older adults presenting for elective surgery may be affected by cognitive dysfunction. The proportion of preoperative cognitively impaired patients turns around 20% to 50% (peaking up to 70% in a study involving vascular surgery patients) [143][144]. Often, cognitive dysfunction is, in fact, undiagnosed in these patients [145]. Yet, baseline cognitive impairment in preoperative older patients is associated with postoperative complications, increased length of stay, and mortality [146]. More specifically, postoperative delirium and postoperative neurocognitive disorder incidence are higher and, by themselves, known to be associated with increased mortality [147][148].

Perioperative anesthetic management must be adapted to the patient's cognitive status. Brain health thus represents a critical concern in older surgical patients and makes pre- and postoperative cognitive screening of utmost importance [149]. 'Perioperative neurocognitive disorders' is a global term referring to either preoperative cognitive impairment, acute postoperative delirium, or postoperative neurocognitive disorder diagnosed up to 12 months after the surgery [150].

Preoperative cognitive testing

To date, there is no consensus on preoperative cognitive assessment. A complete neuropsychological battery would undoubtedly be the best to perform in terms of accuracy, sensitivity, and specificity. However, perioperative daily reality usually does not match time- and resource-consuming tests.

The Montreal Cognitive Assessment (MoCA) was created and validated by Nasreddine and colleagues in 2005 [151]. **Figure 1.6.** shows a French-speaking version. This screening test is easy to administer and takes about ten minutes. The MoCA considerably outperforms the well-known Mini-Mental State Examination in detecting early mild cognitive impairment with a sensitivity of 90% vs. only 18% [151]. It has already been used in the surgical context and has proved to be a reliable and feasible tool to screen for cognitive dysfunction [144][145][152].

The Clock Drawing Test (CDT) is a simple cognitive screening instrument used for over 30 years [153]. The task consists of drawing a circle and placing the hands to indicate ten past eleven [154]. Performed alone, it may help detect moderate or severe dementia, though being less reliable to diagnose milder forms [155]. The CDT is actually a part of numerous cognitive assessments, such as the MMSE or the MoCA. The Mini-Cog also comprises the CDT and a delayed 3-word recall task. Low Mini-Cog scores were shown to predict delirium in the postanesthesia care unit in older patients scheduled for elective surgery under general anesthesia [156].

MONTREAL COGNITIVE ASSESSMENT (MOCA®)
Version 8.1 Français

Nom :
Scolarité : Date de naissance :
Sexe : DATE :

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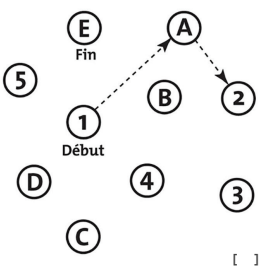

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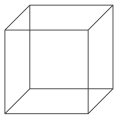

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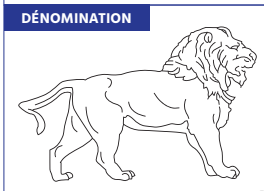
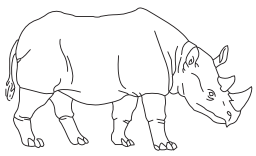
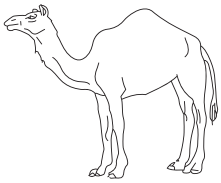

[ ] [ ] [ ]

__/3

MÉMOIRE Lire la liste de mots, le sujet doit la répéter. Faire 2 essais même si le 1er essai est réussi. Faire un rappel après 5 minutes.

	VISAGE	VELOURS	ÉGLISE	MARGUERITE	ROUGE
1ER ESSAI					
2E ESSAI					

PAS DE POINT

ATTENTION Lire la série de chiffres (1 chiffre / sec.). Le sujet doit la répéter dans le même ordre. [ ] 2 1 8 5 4
Le sujet doit la répéter à l'envers. [ ] 7 4 2

__/2

Lire la série de lettres. Le sujet doit taper de la main à chaque lettre A. Pas de points si ≥ 2 erreurs.
[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B

__/1

Soustraire série de 7 à partir de 100. [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65
4 ou 5 soustractions correctes : **3 pts**, 2 ou 3 correctes : **2 pts**, 1 correcte : **1 pt**, 0 correcte : **0 pt**

__/3

LANGAGE Répéter : Le colibri a déposé ses œufs sur le sable. [ ]
L'argument de l'avocat les a convaincus. [ ]

__/2

Fluidité du langage. Nommer un maximum de mots commençant par la lettre « F » en 1 min. [ ] _____ (N ≥ 11 mots)

__/1

ABSTRACTION Similitude entre ex : banane - orange = fruit [ ] train - bicyclette [ ] montre - règle

__/2

RAPPEL — Memory Index Score (MIS)

(MIS)	Doit se souvenir des mots SANS INDICE	VISAGE [ ]	VELOURS [ ]	ÉGLISE [ ]	MARGUERITE [ ]	ROUGE [ ]	Points pour rappel SANS INDICE seulement
X3							
X2	Indice de catégorie						MIS = ____ /15
X1	Indice choix multiples						

__/5

ORIENTATION [ ] Date [ ] Mois [ ] Année [ ] Jour [ ] Endroit [ ] Ville

__/6

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Administré par : _____

Entraînement et certification requis pour assurer la précision.

MIS : /15
(Normal ≥ 26/30)
Ajouter 1 point si scolarité ≤ 12 ans

TOTAL __/30

Figure 1.6. The Montreal Cognitive Assessment (downloaded from https://mocacognition.com/fr/)

Postoperative neurocognitive disorders

Postoperative delirium is a common postsurgical complication in older adults, which is defined as occurring within the first seven postoperative days or until hospital discharge [150]. Confusion Assessment Method (CAM) is the most routinely used test to screen for delirium [157]. Experiencing postoperative delirium may be predictive of future dementia progression, postoperative neurocognitive disorder as well as long-term cognitive decline [158]. Yet, postoperative delirium and postoperative neurocognitive disorder are to be seen as two distinct entities.

'Postoperative neurocognitive disorder' defines a decline in cognitive abilities after surgery, which may be diagnosed between 30 days and up to one year postoperatively [150]. The incidence is highly variable – estimated at around 10% in some studies but rising to 60% after cardiac surgery – depending on the type of surgery, study population, type of cognitive testing, and follow-up periods [159][160]. For diagnostic purposes, three elements must be considered to align with DSM-5 criteria: subjective complaint, objective cognitive impairment, and Instrumental Activities of Daily Living (IADLs). Regarding timing, the more accurate period for cognitive testing is thought to be three months postoperatively [161]. Indeed, this corresponds to the moment when anesthesia, surgery, and hospitalization acute effects would be sufficiently disappeared and thus not interfering. Similarly to preoperative cognitive testing, no consensus exists on which exact instruments to use. The latter should objectively assess the performance in specific cognitive domains [150].

The main goals of this thesis were, first, to evaluate whether olfactory dysfunction could be a reliable predictor of poor postoperative outcome in older patients and, second, to identify the potential underpinning mechanisms linking olfactory impairment and increased death, notably by investigating the connection with frailty, cognition, and telomere length.

SECTION 2 –

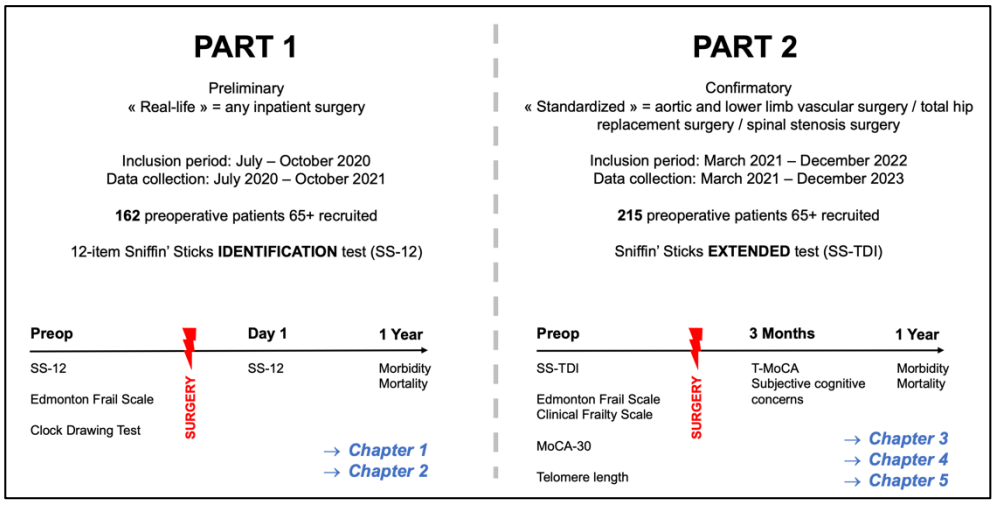
CORRELATION OF OLFACTORY IMPAIRMENT WITH PREOPERATIVE FRAILTY, PERIOPERATIVE INDICATORS OF COGNITION AND POSTOPERATIVE OUTCOME

PART 1 – Preliminary "real-life" study in a group of older patients undergoing all types of inpatient surgeries

Foreword

We began this research project with a deliberately simple protocol, which paved the way for our perioperative olfactory journey. In less than four months, we were able to recruit 162 older patients scheduled for any inpatient elective non-cardiac surgery. We performed a quick olfactory identification test and assessed frailty and cognition with the Edmonton Frail Scale just before surgery. We also tested immediate postoperative olfaction in most of the patients.

This first part of the project had the advantage of quite rapidly delivering strong results, which also helped improve and confirm the robustness of the upcoming larger protocol that we were taking more time to implement.



Comparative table between Part 1 and Part 2 protocols.

Chapter 1. Olfactory Dysfunction Predicts Frailty and Poor Postoperative Outcome in Older Patients Scheduled for Elective Non-Cardiac Surgery

Victoria Van Regemorter[1,2], Jordi Dollase[1,*], Richard Coulie[1,*], Alexandre Stouffs[2], Audrey Dieu[1], Marie de Saint-Hubert[3], André Mouraux[2], Caroline Huart[2,4]

[1]Department of Anesthesiology, Cliniques universitaires Saint-Luc, Brussels, Belgium; [2]Institute of Neuroscience, Université catholique de Louvain, Brussels, Belgium; [3]Department of Geriatric medicine, Centre Hospitalier Universitaire catholique de Louvain Namur, Namur, Belgium; [4]Department of Otorhinolaryngology, Cliniques universitaires Saint-Luc, Brussels, Belgium; [*]Jordi Dollase and Richard Coulie contributed equally to this work

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To access this article

Abstract

OBJECTIVES: Frailty has been suggested to take part in the recently demonstrated link between olfactory dysfunction and overall mortality risk. Preoperative assessment of frailty is essential to detect the most vulnerable patients scheduled for surgery. The aim of this study was to evaluate whether olfactory dysfunction is a reliable predictor of preoperative frailty and postoperative outcome.

DESIGN: This was a single-center prospective observational study conducted between July and October 2020 in Brussels, Belgium.

SETTING AND PARTICIPANTS: 155 preoperative patients aged from 65 years old and scheduled for elective non-cardiac surgery.

MEASUREMENTS: Olfactory function was examined using the Sniffin' Sticks 12-item identification test. Frailty was assessed using the Edmonton Frail Scale (EFS) and handgrip strength. The clock drawing test (CDT) from the EFS was also analyzed separately to evaluate cognitive function. Patients were followed for postoperative complications and mortality over one year.

RESULTS: Olfactory dysfunction was significantly associated with the EFS score, anosmic patients having a higher median EFS score than normosmic patients (6[4-7] vs 4[2-5], p = .025). Anosmic patients had an increased odds of being frail after adjusting for possible confounding factors (OR: 6.19, 95% CI: 1.65-23.20, p = .007) and were more at risk of poor postoperative outcome (including complications and death) (OR: 4.33, 95% CI: 1.28-14.67, p = .018).

CONCLUSIONS: Olfactory dysfunction is associated with preoperative frailty determined by the EFS and with poor post-surgical outcome at one-year.

Key words: olfaction, frailty, Edmonton frail scale, clock drawing test, postoperative complications

Introduction

Olfactory dysfunction is defined as impaired ability to smell, which may be moderate (hyposmia) or severe (anosmia). This sensory loss, though rarely evaluated clinically, increases in frequency with age making it quite common in the older population [14]. Recently, olfactory dysfunction was shown to be predictive of overall mortality in older adults [61][65][63]. The greater risk of death depended on the severity of the olfactory dysfunction, with anosmic subjects having a higher tendency to die than their hyposmic peers, which in turn were more likely to die than normosmic individuals [61]. The reasons behind this association are still unclear and may comprise neurodegenerative diseases, a direct effect of olfactory dysfunction on nutrition, danger warning and social interaction, general poor health and, last but not least, accelerated brain aging which in fact represents a lowered physiologic repair function [12]. When evaluating risk in older adults, frailty status is currently considered as more relevant than chronological age and medical comorbidities, because frailty status relates to available physiological reserves [140]. In particular, preoperative assessment of frailty is crucial to detect the most vulnerable patients scheduled for a surgical intervention [126]. Surgery acts as a heavy physical stressor, making frail patients at greater risk of perioperative complications and mortality (8). So far, only a few studies investigated olfactory dysfunction in light of frailty status, making evidence still sparse [103][104][107][162][163]. Besides, no such study has ever been conducted in a population of preoperative older adults.

The aim of this study was to evaluate whether olfactory dysfunction assessed using the Sniffin' Sticks 12-item identification test is associated with preoperative frailty and postsurgical outcome.

Method

Study Population and design

We conducted a prospective observational study at the Cliniques universitaires Saint-Luc (Brussels, Belgium) between July and October 2020. The study protocol was approved by the institutional Ethics Committee (2020/22JAN/050) and was registered on https://clinicaltrials.gov/ (NCT04700891). Written informed consent was obtained from all participants after receiving an explanation of the study.

The study included preoperative patients aged from 65 years old and scheduled for inpatient minor, intermediate or major elective non-cardiac surgery under general anesthesia (classified as such according to the European Society of Anaesthesiology cardiovascular assessment guidelines) [164]. All types of surgeries were considered with the exception of cardiac, head and neck surgery. Patients were selected by looking into the surgical program and excluded at screening if they had a history of neurological or psychiatric disorder, severe head trauma, chronic rhinosinusitis, post-infectious olfactory loss, current acute upper respiratory tract infection or any history of past or current COVID-19 infection. Refusal rate among potential participants was about 5-10%. Out of the 167 patients initially included, 5 were excluded at screening (meeting of an exclusion criteria) and 7 did not effectively undergo surgery under general anesthesia, resulting in a final sample size of 155 patients. Olfactory and frailty assessments were performed on the day before surgery. The information collected included demographic variables, education level, smoking status, age-adjusted Charlson comorbidity index, American Society of Anesthesiologists (ASA) physical status, history of active neoplasia and chemotherapy, and number of daily medications since it is acknowledged that these variables may interfere with olfaction and/or morbimortality. We also reported grade and duration of surgery.

Olfactory function assessment

Olfactory function was assessed using the Sniffin' Sticks 12-item identification test (Burghart Messtechnik GmbH, Wedel, Germany), which is a validated psychophysical testing method [25]. The 12 odors were presented to the patients using pen-like odor dispensing devices placed approximately 2cm in front of the nostrils. The patients were asked every time to make a forced choice from lists of four descriptors each. For each correct answer, one point was awarded and points were added to obtain an olfactory score ranging from 0 to 12. They were then classified in three groups according to their score: anosmia (≤6), hyposmia (7-10) and normosmia (≥11). The assessment of olfactory function based solely on the Sniffin' Sticks 12-item identification test was chosen to allow a rapid assessment that could be implemented as a routine clinical test [25].

Outcome measures

Evaluation of frailty status

The Edmonton Frail Scale (EFS) was used to determine frailty status of each patient by evaluating nine domains: functional performance, cognitive function, general health, functional independence, social support, used medications, nutrition, mood and continence. The EFS is an instrument which can be administered quickly by non-geriatricians [132]. It has been validated with respect to geriatric specific screening tools [133] and is considered one of the most appropriate preoperative frailty assessment tool [128]. Test results range from 0 to 17 points, a higher score representing a higher level of frailty. The cut-off value for frailty was defined as ≥6/17 [133].

The cognitive assessment of the EFS consists of a clock drawing test (CDT) in which the circle of the clock face is already provided. The patients are asked to put in all the numbers and to set the hands to 10 after 11. Besides the EFS

evaluation, each clock was scored using Rouleau's scale [154] in which 8 is the maximum score and represents the best performance. We defined the patients as either "cognitively intact" (score of ≥6/8) or "cognitively impaired" (score of ≤5/8).

Maximal handgrip strength was measured to evaluate maximum voluntary hand force using a digital Jamar-type handgrip dynamometer on both hands. The highest of the two measures was used. Handgrip strength is known to be significantly associated with sarcopenia and frailty [165].

Evaluation of postoperative complications and mortality

Patients were followed for postoperative complications and mortality during one year after the date of the surgery, using the Clavien-Dindo classification [141]. Grade 1 complications (defined as minor risk events not requiring specific therapy) were not considered as meaningful events. Grade 2 to 4 were listed as "complications". Grade 5 corresponded to "death of the patient". Complication and death events were grouped as "poor outcome". The data was obtained using local hospital medical records and the Belgian health network (if the patients had authorized this medical record sharing) which allows an overall view of patients' medical information.

Study endpoints

The endpoints of this study were : (1) to evaluate the association between olfactory identification function using the Sniffin' Sticks 12 item identification test and, on the one hand, the EFS score, on the other hand, performance at CDT, (2) to assess whether olfactory identification function is a predictor of postoperative complications and mortality at one-year and to examine its potential added value to frailty evaluation on postoperative outcome prediction.

Statistical analysis

Data were analyzed using SPSS version 27.0. The Kolmogorov-Smirnov test was used to check the normality of the data. Ordinal and continuous data were not normally distributed and were expressed as medians (interquartile range). Nominal variables were compared between frail and non-frail patients with a Pearson χ^2 test whereas ordinal and continuous data were compared using a Mann-Whitney U-test. Baseline patient characteristics which were significant in the univariable analysis at a threshold p value < .1 were entered into a multivariable logistic regression model to predict the presence of frailty. Age and gender were also added to the model given their known relationship with the outcome and the other variables. A Kruskal-Wallis test was used to compare the EFS score between categories of olfactory function. A Pearson χ^2 test was used to compare clock drawing test performance between categories of olfactory function and multivariable logistic regression was used to predict poor cognitive performance. Prediction of poor outcome at one year after surgery was analyzed with binary logistic regression. We compared the performance of the olfactory score and the EFS score to predict poor postoperative outcome by building up receiving operating characteristic (ROC) curves. Logistic regression models and ROC curves were adjusted for age and sex. Any p value < .05 was considered significant.

Results

Study population

We included a total of 155 preoperative patients with a median age of 73 years (68-78) and whereof 94 (60.6%) were female patients (**Table 2.1.**). 57 patients (36.8%) were categorized as frail before surgery. Body mass index, education level, smoking status, the presence of active neoplasia or recent chemotherapy

did not differ between frail and non-frail patients. There was a tendency to a higher age-adjusted Charlson comorbidity index score in frail patients (p = .089). In the frail group, 34 patients (59.6%) were classified ASA physical status III or IV whereas they were only 39 (39.8%) in the non-frail group (p = .017). Median number of daily medications was significantly higher in frail patients (p = .002). Overall, 44 patients (28.4%) had minor surgery, 96 (61.9%) had intermediate surgery and 15 (9.7%) had major surgery, and these proportions were similar across frailty groups. Median duration of surgery was not different between frail and non-frail patients.

Characteristic	Overall patients (n=155)	Non-frail patients (EFS < 6) (n=98)	Frail patients (EFS ≥6) (n=57)	p Value
Age (y)	73 (68-78)	72 (68-77)	74 (69-80)	.266
Female (%)	94 (60.6)	56 (57.1)	38 (66.7)	.242
Body mass index	26.3 (23.4-30.1)	26.8 (23.3-30.5)	25.3 (23.3-29.6)	.424
Lower education level (%) (≤ 9 years)	71 (45.8)	41 (41.8)	30 (52.6)	.151
Smoking				.500
Non smoker (%)	88 (56.8)	54 (55.1)	34 (59.7)	
Former Smoker (%)	49 (31.6)	34 (34.7)	15 (26.3)	
Present smoker (%)	18 (11.6)	10 (10.2)	8 (14.0)	
Olfactory function				.022
Normosmia	32 (20.6)	26 (26.5)	6 (10.5)	
Hyposmia	101 (65.2)	62 (63.3)	39 (68.4)	
Anosmia	22 (14.2)	10 (10.2)	12 (21.1)	
Number of daily medications	4 (3-7)	4 (2-6)	6 (4-8)	.002
Active neoplasia (%)	57 (36.8)	38 (38.8)	19 (33.3)	.498
Chemotherapy in the past year (%)	25 (16.1)	13 (13.3)	12 (21.1)	.204
Age-adjusted Charlson comorbidity index score	4 (3-6)	4 (3-5)	5 (3-7)	.089
ASA physical status				.017
I-II (%)	82 (52.9)	59 (60.2)	23 (40.4)	
III-IV (%)	73 (47.1)	39 (39.8)	34 (59.6)	
Grade of surgery				.843
Minor (%)	44 (28.4)	29 (29.6)	15 (26.3)	
Intermediate (%)	96 (61.9)	59 (60.2)	37 (64.9)	
Major (%)	15 (9.7)	10 (10.2)	5 (8.8)	
Duration of surgery (min)	152 (107-222)	155 (106-227)	150 (107-219)	.936

Note. EFS = Edmonton Frail Scale; ASA = American Society of Anesthesiologists

Table 2.1. Baseline and operative characteristics of preoperative patients according to their frailty status (evaluated by the Edmonton Frail Scale).

Association between preoperative olfactory function and frailty

Out of the whole study population, 32 patients (20.6%) were classified as normosmic, 101 (65.2%) as hyposmic and 22 (14.2%) as anosmic. We found that preoperative olfactory function differed significantly according to frailty

status as defined by the EFS (p = .022). 21.1% of the frail patients (12/57) were anosmic compared to only 10.2% of the non-frail patients (10/98). Parallel to this, there was a higher proportion of normosmic patients in the non-frail group (26.5%) in comparison to the frail group (10.5%).

Moreover, the EFS score was significantly related with the identification of olfactory dysfunction: anosmic patients had a significantly higher median EFS score than normosmic patients (6[4-7] vs 4[2-5], p = .025) (**Figure 2.1.**).

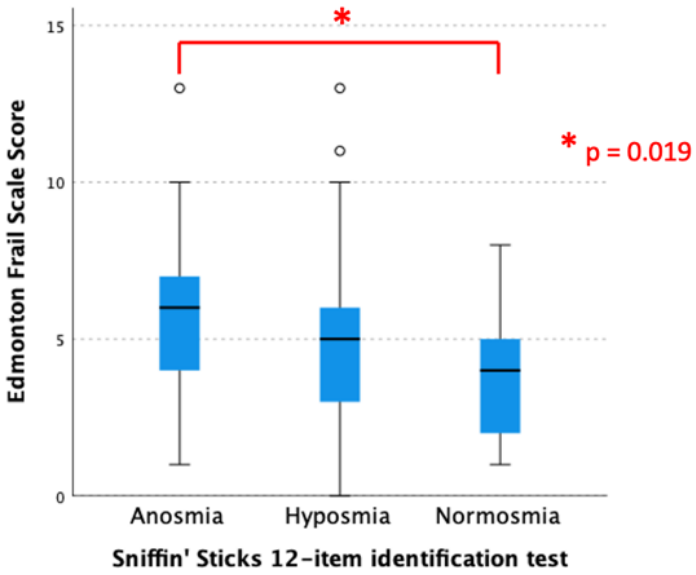


Figure 2.1. Edmonton Frail Scale score according to preoperative olfactory function.

Multivariable logistic regression analysis was performed to associate olfactory function and the presence of preoperative frailty, while adjusting for other significant (p value < .1 in the univariable analysis) baseline patient characteristics. The results are summarized in **Table 2.2.** When adjusting for age, gender, comorbidities, ASA physical status and number of daily medications, we found that anosmic patients still had an increased odds of being

frail (odds ratio [OR]: 6.19, 95% CI: 1.65-23.20, p = .007). Hyposmia, however, failed to remain significantly associated with frailty.

Variable	Univariable			Multivariable		
	OR	95% CI	p Value	OR	95% CI	p Value
Olfactory identification function						
Anosmia	5.20	1.53-17.64	.008	6.19	1.65-23.20	.007
Hyposmia	2.73	1.03-7.22	.044	2.55	0.89-7.26	.081
Baseline characteristic						
Age	1.03	0.98-1.08	.220	1.02	0.97-1.08	.466
Female	1.50	0.76-2.96	.243	2.16	0.98-4.79	.058
Age-adjusted Charlson comorbidity index score	1.14	0.99-1.30	.067	1.01	0.84-1.20	.932
ASA physical status III-IV	2.24	1.15-4.35	.018	2.11	0.90-4.91	.085
Number of daily medications	1.16	1.05-1.29	.005	1.16	1.03-1.31	.014

Note. OR = Odds Ratio; CI = Confidence Interval; ASA = American Society of Anesthesiologists

Table 2.2. Univariable and multivariable logistic regression analysis for prediction of preoperative frailty, including preoperative olfactory identification function, age, gender and baseline characteristics whose level of significance reached p value < .1 in the univariable analysis.

The median maximum handgrip strength of normosmic patients (32.7kg) was greater than that of hyposmic and anosmic patients (23.9kg and 26.0 kg), but this difference was not significant.

Association between preoperative olfactory function and performance at clock drawing test

Olfactory dysfunction was also associated with performance at CDT ($\chi^2(2)$ = 8.507, p = .014). The results are shown in **Figure 2.2.** 63.6% of anosmic patients against only 25% of normosmic patients were categorized as “cognitively impaired” based on the CDT score. Even when controlling for education level in a multivariable logistic regression model, anosmia was still predictive of lower performance at CDT (OR: 4.37, 95% CI: 1.22-15.68, p = .024).

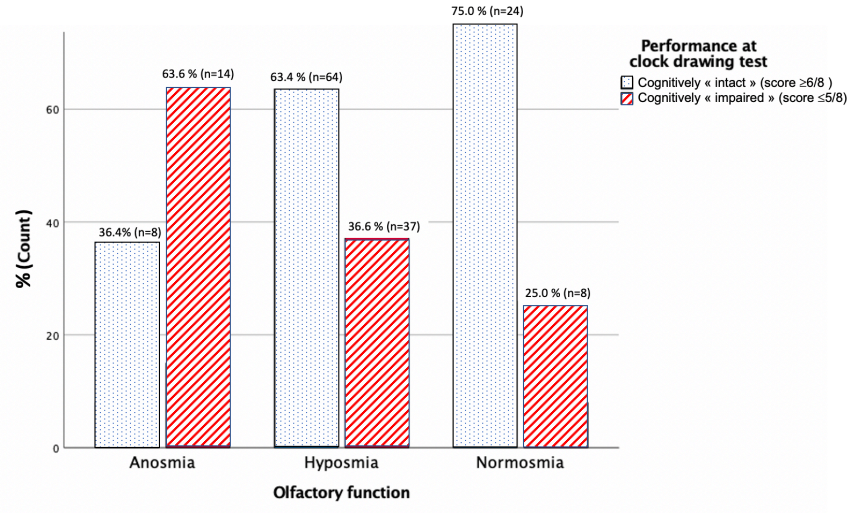


Figure 2.2. Performance at clock drawing test according to preoperative olfactory function.

Association between preoperative olfactory function and outcome after surgery

Within one year after surgery, 43 patients (28.1%) presented at least one postoperative complication and 9 patients (5.9%) died. Among the 22 anosmic patients, 9 (40.9%) suffered from a postoperative complication and 2 (9.1%) died. Among the 101 hyposmic patients, 29 (29.3%) had a complication and 6 (6.1%) were dead. Only 1 (3.1%) of the 32 normosmic patients died and only 5 (15.6%) presented a postoperative complication.

In a logistic regression analysis, anosmic patients were found to be more at risk of poor postoperative outcome (which comprised complications or death) than normosmic patients (OR: 4.33, 95% CI: 1.28-14.67, p = .018) (**Figure 2.3.**, Model 1). When we controlled for frailty (using Edmonton Frail Scale score) in Model 2, the effect of anosmia on poor outcome was decreased and did not reach statistical significance (OR: 3.04, 95% CI: 0.86-10.78, p = .086). However, the addition of an interaction term between olfactory function and frailty had no effect

on this model. In Model 3, we adjusted for comorbidities (using age-adjusted Charlson comorbidity index), which lowered only slightly the effect of anosmia on poor outcome (OR: 3.76, 95% CI: 1.08-13.07, p = .037).

We carried out ROC curve analyses for the EFS and the olfactory score to evaluate their respective performance in predicting poor postoperative outcome. The ROC curves showed similar patterns, displaying an area under the curve (AUC) of 0.669 for both the EFS and the olfactory score. In our study, the positive predictive value (PPV) of the EFS for having poor postoperative outcome was 48.2% and the negative predictive value (NPV) of not developing postoperative complication or death was 74.2%. Yet, the PPV increased to 66.7% if the frail patients were also classified as anosmic and the NPV increased to 84.6% if the patients were both non-frail and normosmic.

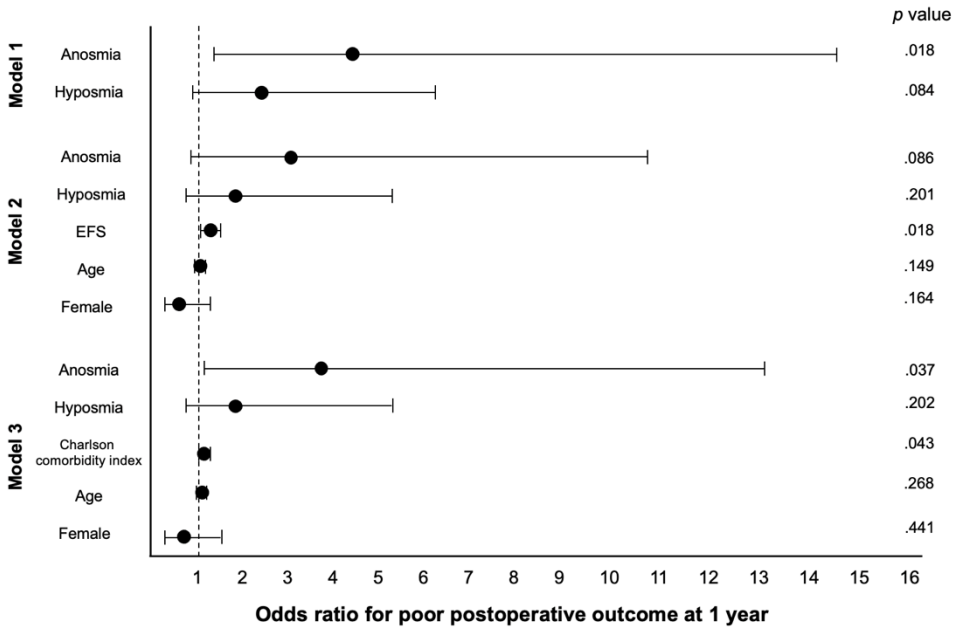


Figure 2.3. Odds ratio and 95% confidence intervals of logistic regression models predicting poor postoperative outcome at 1 year from preoperative olfactory dysfunction (Model 1). Data were adjusted for age and gender, for Edmonton Frail Scale score (Model 2) and for age-adjusted Charlson comorbidity index score (Model 3).

Discussion

This study is the first prospective observational study to investigate the relationships between preoperative olfactory function, preoperative frailty and postsurgical outcome in older patients. First, we show that preoperative olfactory dysfunction (assessed using the Sniffin' Sticks 12-item identification test) is associated with preoperative frailty determined by the EFS and with poorer cognitive performance in a population of older patients evaluated before they undergo elective surgery. Our study also demonstrates a relationship between olfactory dysfunction and poor postoperative outcome. Importantly, the predictive value of the EFS on poor postoperative outcome was improved by taking into account anosmia or normosmia classification.

Depending on age, tests and cut-offs used, frequency of olfactory dysfunction differs a lot and may concern up to 3 out of 4 older adults [32]. Among our cohort, we found 65.2% hyposmic patients and 14.2% anosmic patients using the Sniffin' Sticks 12-item identification test.

There was a clear link between olfactory function and the preoperative EFS score, anosmia being associated with preoperative frailty and normosmia being more prevalent in robust patients. Previous studies exploring smell and frailty are sparse and may present methodological weaknesses [163]. A first study conducted in 768 Japanese community-dwelling adults aged ≥ 65 years failed to find a significant association between self-assessed olfactory dysfunction and a modified Fried's frailty criteria [103]. Another study including 1035 Italian subjects of the same age range showed a relationship between self-assessed olfactory dysfunction and Fried's frailty criteria [107]. Both these studies suffer from the subjectivity of self-assessing olfaction [16]. Harita et al used a Japanese-adapted 12-item identification test in 141 community-dwelling older adults. They found a significant correlation between olfactory impairment and the Study of Osteoporotic Fractures index of frailty [104]. Lastly, Bernstein et al also

demonstrated a strong association between olfactory dysfunction (examined with an 8-item identification test) and a 39-item frailty index in their study totalizing 3547 participants aged ≥ 40 years [162]. These two latter studies were cross-sectional studies and data were reported by the participants, which could have led to some biases.

Nevertheless, our results are in line with those data and thus contributes to the validation of olfactory dysfunction as being associated with frailty. In the multivariable model, we controlled for comorbidities and for ASA physical status which did not attenuate the relationship between anosmia and frailty. Harita et al also found that the results were not modified by adjusting for health-related confounding factors [104].

Olfactory dysfunction is a well-known biomarker for neurodegenerative diseases, suggesting more largely a substantial link with cognition [46,48]. In our study, anosmic preoperative older adults were more likely to exhibit lower scores at CDT, which supports the possibility that olfactory dysfunction may relate to preoperative cognitive impairment. Recently, the concept of cognitive frailty has emerged associating physical frailty and cognitive impairment [166]. The two latter are thought to share the same mechanisms and to both lead to poor outcome [167]. Therefore, this might account for the fact that olfactory dysfunction is associated with both frailty and cognitive impairment in our data.

In our cohort, over the year that followed surgery, 28.1% of the patients developed a complication and nearly 6% died. Obviously, the figures of perioperative morbidity and mortality varies greatly in the literature according to type of surgeries, the type of patients and the urgency of surgery. Given our “real-life” older population, the wide range of surgeries performed with an elective setting, these outcome data seem comparable to other studies [168,169,170]. Importantly, we show that anosmia is a predictor of poor postoperative outcome. In our cohort, the small number of death events

precludes any valuable conclusion on its own. Yet, regarding complications, incidence was 2.5 times higher in anosmic than in normosmic patients.

The present results in a perioperative context brings more evidence to the previously described link between olfactory dysfunction and mortality [12]. Also, our results may shed some light on the underlying mechanisms. Controlling for frailty in the prediction of poor postoperative outcome strongly decreased the effect of anosmia on postsurgical outcome. We also adjusted for comorbidities in a different model, which had in this case less effect on anosmia. In a study including 125 older patients undergoing elective surgery, it was found that age and the EFS score were the only variables to remain statistically significantly associated to postoperative complications, unlike various medical comorbidities [171]. All this suggests a prominent role of frailty in mediating the association between olfactory dysfunction and bad outcome. On the other hand, the effect of general poor health, that is, suffering from multiple comorbidities, seems of less importance.

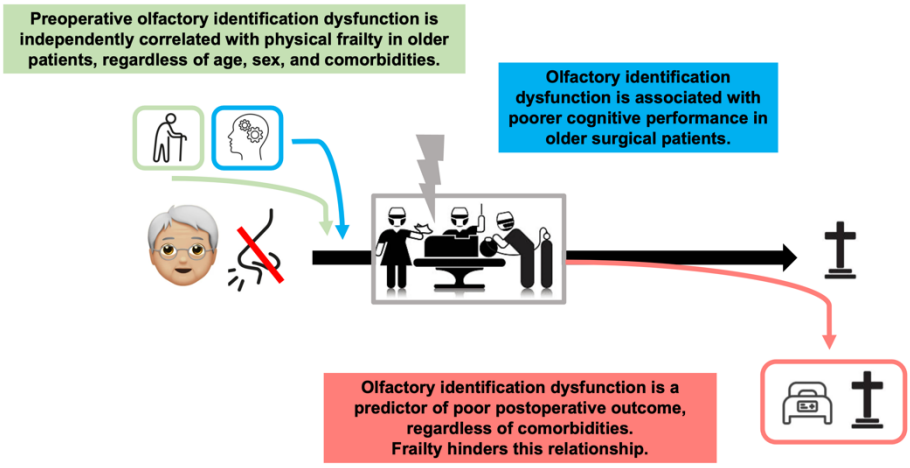
Not surprisingly, we noted a quite poor performance of both the EFS and the Sniffin' Sticks 12-item identification test when building ROC curves to further predict the presence of poor postoperative outcome. Obviously, postoperative outcome does not depend exclusively on frailty. Furthermore, frailty assessment will always remain tricky, explaining why so many different frailty instruments currently exist in the literature without a single one being truly a silver bullet. What is more interesting was the added value of anosmia or normosmia on the predictive values of the EFS. Olfactory testing, as a quick bedside tool, demonstrates here its potential clinical value and could thus add up to the available battery of frailty tests.

It is important to recognize some limitations of our study. First, our cohort may suffer from a small sample size, which limited power in some analyses, notably concerning 1-year mortality rate. Second, our preoperative population as well as the type of surgery was very diversified and may lack standardization in order to

improve specificity in the outcome results. Third, follow-up was based on chart review and may thus have missed some postoperative events. Finally, patients did not systematically take a COVID-19 PCR-test before surgery, which could have led to some confounding bias regarding olfactory function.

Conclusion

In conclusion, we bring new evidence regarding the link between olfaction, frailty and postoperative outcome. Olfactory dysfunction is definitely associated with preoperative frailty, which, in turn, seems to play a key role in mediating the relationship between olfactory dysfunction and poor outcome. From a clinical perspective, quick assessment of olfactory status seems to improve the performance of frailty evaluation in the prediction of postsurgical outcome. Larger prospective studies with more standardized population are needed to strengthen these findings.



Graphical summary of the main findings from Chapter 1.

Chapter 2. Poor preoperative performance at Clock Drawing Test is associated with postoperative decline in olfaction in older patients: an observational pilot study

Victoria Van Regemorter[1,2], Richard Coulie[1,*], Jordi Dollase[1,*], Mona Momeni[1,2], Alexandre Stouffs[2], Lisa Quenon[2,3], André Mouraux[2], Caroline Huart[2,4]

[1]Department of Anesthesiology, Cliniques universitaires Saint-Luc, Brussels, Belgium; [2]Institute of Neuroscience, Université catholique de Louvain, Brussels, Belgium; [3]Department of Neurology, Cliniques universitaires Saint-Luc, Brussels, Belgium; [4]Department of Otorhinolaryngology, Cliniques universitaires Saint-Luc, Brussels, Belgium; [*]Richard Coulie and Jordi Dollase contributed equally to this work

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To access this article

Abstract

Background: Decline in olfaction may occur after general anesthesia, but the exact incidence and underlying physiopathology remain scarcely investigated. Olfactory dysfunction arises with aging and is known to be linked to cognitive impairment. In this pilot study, we evaluated the incidence of immediate postoperative decline in olfaction and its association with a preoperative cognitive test, performance at Clock Drawing Test (CDT), in a group of older patients.

Methods: This pilot study is a sub-analysis of a prospective observational study. Patients ≥ 65 years old and scheduled for elective non-cardiac surgery under sevoflurane-based anesthesia were enrolled. CDT was part of the preoperative evaluation. We assessed olfaction on the day before and the day after surgery (between 16 and 26 hours postoperatively) using the Sniffin' Sticks 12-item identification test, which consists of pen-like devices displaying 12 different odors. Postoperative decline in olfaction was defined as a decrease of at least 1 standard deviation in the olfactory score.

Results: We included a total of 93 patients, among whom 19 (20.4%) presented a postoperative decline in olfaction. The incidence of postoperative decline in olfaction was higher in the "CDT low-score" (score ≤5/8) group (11/34, 32.4%) than in the "CDT high-score" (score ≥6/8) group (8/58, 13.6%) (P = 0.030). Despite adjusting for confounding variables, CDT score remained independently associated with immediate postoperative decline in olfactory identification function (OR 0.67, 95% CI 0.48 to 0.94, P = 0.022).

Conclusions: Postoperative decline in olfaction occurred in 20.4% of older patients and was associated with poor preoperative performance at CDT.

Trial Registrations: This study was retrospectively registered on https://clinicaltrials.gov/ under the NCT04700891 number (principal investigator : Victoria Van Regemorter), in December 2020.

Keywords : Olfaction, Clock Drawing Test, aged, preoperative cognitive function, postoperative complications

Background

The sense of smell contributes to social communication, guides nutrition behavior and is crucial to detect daily life hazards [13]. Olfactory dysfunction may thus have a severe impact on health and quality of life. Incidence of olfactory dysfunction increases with age, as a result of several mechanisms: exposure to toxins or drugs, infection, trauma, but also brain aging and neurodegenerative diseases [12,172].

Decline in olfactory function has been reported as a complication of general anesthesia for all types of surgeries, however its frequency and physiopathology remain largely unknown. Several reports have been published over the years, mainly describing isolated cases of patients with sudden postoperative onset of medium to long-lasting olfactory or gustatory dysfunction .[173,174,175,176,177]. On the other hand, some small-sized studies have shown a possible detrimental effect of the use of sevoflurane compared to other anesthetic agents on immediate postoperative olfactory function [178,179,180,181]. In a recent study, age was correlated to poorer postoperative olfactory performances, thereby suggesting interactions between cognitive impairment, which is more prevalent with age [182], and olfactory dysfunction [183].

To evaluate the incidence of immediate postoperative decline in olfaction and to address whether it is associated with preoperative cognitive performance, we performed a pilot study. We realized a sub-analysis of a previously published prospective observational study in older patients undergoing various types of elective non-cardiac surgery under sevoflurane-based anesthesia [184]. We hypothesized that preoperative performance at the Clock Drawing Test (CDT) – which engages multiple cognitive functions, including visuoconstructive abilities, executive function and semantic memory [185], and is used for the preoperative assessment of cognition [186] – would be related to postoperative decline in

olfactory identification score. Moreover, we aimed at investigating the potential relationship between intraoperative administered drugs doses and worse postoperative olfaction.

Methods

Study population and protocol

This pilot study is a sub-analysis of a prospective observational study conducted at the Cliniques universitaires Saint-Luc (Brussels, Belgium) between July and October 2020 [184]. The whole study protocol was approved (2020/22JAN/050) by the institutional Ethics Committee of Cliniques universitaires Saint-Luc, Université catholique de Louvain, Brussels, Belgium (Chairperson J.-F. Maloteaux) on 3 March 2020. At that time, the authors were not aware of the recommendation to register prospective observational studies. It was therefore registered retrospectively on https://clinicaltrials.gov/ under the NCT04700891 number (principal investigator : Victoria Van Regemorter, https://beta.clinicaltrials.gov/study/NCT04700891), in December 2020. All participants gave their written informed consent. This manuscript adheres to the applicable STROBE guidelines.

The complete study protocol has been described previously [184]. The aims of the primary trial were to correlate preoperative olfactory identification function with frailty and cognitive performance, assessed by the CDT, as well as with postoperative outcome. Inclusion criteria were patients aged ≥ 65 years old who were scheduled for all minor, intermediate or major inpatient non-cardiac surgery under sevoflurane-based anesthesia. Head and neck surgery patients were not included since postoperative olfactory dysfunction may occur as a surgical complication. Exclusion criteria were as follows: history of neurological (including any type of diagnosed dementia) or psychiatric disorder, severe head trauma, chronic rhinosinusitis, post-infectious olfactory dysfunction or current acute

upper respiratory tract infection. Any history of past or current COVID-19 infection was also an exclusion criterion, which was verified either by a PCR-test taken just before the surgery or by interrogating the patient about any related symptoms, especially, any recent change in smell or taste abilities.

We performed preoperative and postoperative olfactory assessments. Preoperative olfactory testing was realized on the day before surgery and was also accompanied by a frailty assessment including an evaluation of cognitive performance. Postoperative olfactory testing was realized on the day after the surgery, so that all patients took their test between 16 and 26 hours after their surgery. In order to get the same conditions for pre- and postoperative tests, both were realized in the patient's room. Three physicians were trained specifically together to administer the tests in the exact same way and always made sure to get a calm and uninterrupted testing session with the patients. None of the patients tested postoperatively were delirious when the olfactory test was carried out.

All patients received general anesthesia with intravenous induction followed by maintenance with sevoflurane. Induction agents were left to the discretion of the anesthesiologist in charge of the patient. Sevoflurane maintenance dose was adjusted by achieving end-tidal concentration equivalent to 1 age-adjusted MAC. All the patients received proper routine intraoperative care using an individualized approach depending on each patient's comorbidities. Vasopressors were administered whenever needed to maintain adequate hemodynamics. Protective ventilation was administered to all patients and the target for end-tidal carbon dioxide ranged between 35 and 45 mmHg. Normothermia was maintained with forced-air warming or fluid warming systems. Patients were extubated at the end of the surgical procedure then transferred to the post-anesthesia care unit. We did not record any intra-or postoperative major event regarding hemodynamics or ventilation. No patient was admitted to the intensive care unit in the immediate postoperative period.

Predictor variables

All patients had a preoperative frailty evaluation with the Edmonton Frail Scale, since constituting the primary outcome of the initial study [184]. In this sub-analysis, we focused on the Clock Drawing Test (CDT), which is part of the Edmonton Frail Scale, as preoperative cognitive testing. In this test, the circle of the clock was already provided, and the patients were asked to put in all the numbers, then to set the hands to 10 after 11 [132]. The CDT increases total Edmonton Frail Scale score by one point for minor spacing errors and by two points for other errors. However, to improve scoring accuracy, each clock was also scored separately from the Edmonton Frail Scale using Rouleau's scale [154], in which 10 is the maximum score and represents the best performance. A score of ≤7/10 usually indicates significant cognitive impairment [155]. Indeed, normative data obtained for French-Quebec healthy older adults confirmed that the score of 7 represents at most the 10th percentile in the oldest, thus reflecting at least mild cognitive impairment [187]. Here, we removed the two points originally awarded for the adequate drawing of the clockface from both the total score and the cut-off. Patients were thus categorized in the "CDT high-score" group when their score was 6 or more or in the "CDT low-score" group when scoring ≤5/8.

Moreover, we recorded the doses of anesthetic as well as analgesic intravenous drugs administered intra- or postoperatively in our patients and suspected to have a potential influence on olfactory function [54,176,188]. Duration of surgery, reflecting duration of sevoflurane exposure, was also reported. Other information collected included demographic variables, education level and American Society of Anesthesiologists (ASA) physical status. Grades of the surgeries were classified according to the European Society of Anesthesiology cardioavascular assessment guidelines [164].

Outcome variable

Olfactory function assessment

Olfactory function was evaluated with a validated psychophysical testing method that is the Sniffin' Sticks 12-item identification test (Burghart Messtechnik GmbH, Wedel, Germany), which does not include the evaluation of the threshold and discrimination modalities of olfactory function. This olfactory identification test consists of pen-like odor dispensing devices displaying 12 different odors (see **Figure 2.4.**), namely orange, leather, cinnamon, peppermint, banana, lemon, licorice, coffee, cloves, pineapple, rose and fish. The pens were consecutively placed approximately 2cm in front of the nostrils for approximately 3 s, and the patients were then asked to make a forced choice from lists of four descriptors each. The descriptors were written down on cards presented in front of the patient. For each correct answer, one point was awarded and points were added to obtain a final olfactory score ranging from 0 to 12. Since there is a 25% probability of a random correct answer for each pen, chance by itself would already provide on average a total score of 3 points out of 12. Patients scoring 3 or less at preoperative olfactory test were excluded.

The preoperative and postoperative olfactory identification tests were identical. To minimize test-retest bias, the patients were not told about their test results during the preoperative assessment. We calculated postoperative change in olfactory identification score as the numerical difference of postoperative olfactory identification score minus preoperative olfactory identification score. We then defined postoperative decline in olfactory identification score as a decrease of at least 2 points (corresponding to one standard deviation relative to the average change across all patients). Conversely, a better postoperative performance in olfactory identification

score was characterized as an increase of at least 2 points (i.e. one standard deviation). A difference of zero or one point was considered unsignificant change.

Figure 2.4. The Sniffin' Sticks 12-item identification test (Burghart Messtechnik GmbH, Wedel, Germany). This test consists of 12 pen-like odor dispensing devices, each displaying a different odor. The patient is asked each time to make a forced choice from a list of 4 descriptors. Total olfactory score ranges from 0 to 12 points, where 12 is the best score.

Statistical analysis

The main objectives were to assess the incidence of postoperative decline in olfactory identification function and to evaluate its association with preoperative

performance at CDT, as cognitive testing. Furthermore, we analyzed the association of intraoperative drugs doses with postoperative decline in olfactory identification function. We did not realize any power analysis for the aims of this pilot study since it was considered exploratory. Data were analyzed using SPSS version 27.0. The Kolmogorov-Smirnov test was used to check the normality of the data. Continuous data were not normally distributed and were expressed as medians (interquartile range). Comparisons between the "CDT high-score" group and the "CDT low-score" group were realized with a Pearson χ^2 test for nominal variables and with a Mann-Whitney U-test for continuous variables. We used univariable and multivariable binary logistic regression analyses to assess the relationship between CDT score and the presence of postoperative decline in olfactory identification score. For these regression analyses, we considered any potential confounding variables regarding olfactory function (age, gender) or postoperative cognitive function (level of education, ASA physical status, surgery grade). The secondary objective was to compare intraoperative drugs doses between the patients who presented a postoperative decline in olfactory identification function and the patients who did not. Continuous data were compared using a Mann-Whitney U-test. The presence of patient-controlled intravenous analgesia in the ward was compared with a Pearson χ^2 test. Any *P* value < 0.05 was considered significant.

Results

We finally included 93 patients for the purposes of this pilot study (see flowchart on **Figure 2.5.**). In total, when considering the whole cohort, median preoperative olfactory identification score was 10 [8,11] compared to 9 [8,11] after the surgery. Individual postoperative change in olfactory identification scores is detailed in **Figure 2.6A.** Among all patients, 19 (20.4%) presented a postoperative decline in their olfactory identification, making from 2 to 4 more errors compared to their preoperative test. 68 patients (73.1%) did not

significantly change their postoperative score. A better postoperative performance was only observed in 6 (6.5%) patients who increased their olfactory score by 2 to 4 points.

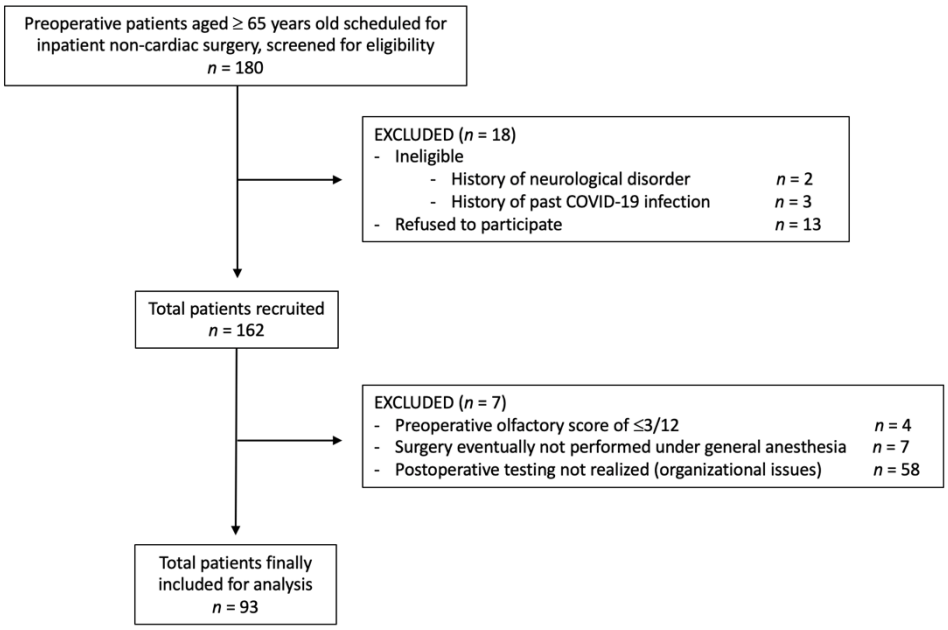


Figure 2.5. Study Flowchart. This pilot study is a sub-analysis of a prospective observational study. Final sample size is 93 patients.

Baseline and operative characteristics of all the patients are summarized in **Table 2.3.** Median age was 72 years old [68,78] and women comprised 58.1% of the cohort. Patients were classified in two groups according to their preoperative performance at CDT, as described beforehand. Age, gender and body mass index were similar between the two groups. Among the “CDT low-score” group, 52.9% of patients (18/34) had a lower education level whereas they represented only 32.2% (19/40) of the “CDT high-score” group (P = 0.049). ASA physical status and grades of surgeries also did not differ significantly.

Preoperative performance at the CDT was associated with postoperative decline in olfactory identification (χ^2 (1) = 4.69, P = 0.030). The results are shown in

Figure 2.6B. 32.4% of the patients in the "CDT low-score" group (11/34) presented a postoperative decline in olfactory identification against only 13.6% (8/59) in the "CDT high-score" group.

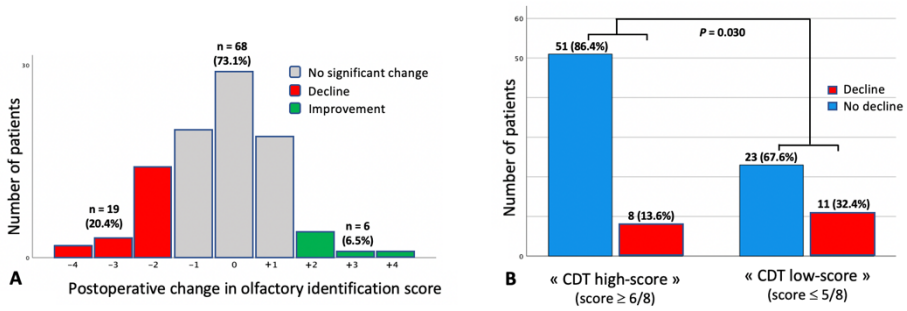


Figure 2.6. Postoperative change in olfactory identification score. (**A**) Individual distribution. The axis line of the histogram represents the numerical difference of postoperative minus preoperative olfactory identification score. (**B**) Comparison according to preoperative performance at Clock Drawing Test. The "Decline" category represents patients showing a postoperative decline in olfactory identification score of at least one standard deviation (corresponding to a 2 point decrease). The "No decline" category gathers patients presenting either no significant postoperative change or a postoperative increase in olfactory identification score. CDT, Clock Drawing Test.

Characteristics	"CDT high-score" group ($n = 59$)	"CDT low-score" group ($n = 34$)	*P* Value
Age, year	72.0 [68.0, 78.0]	72.5 [69.0, 77.0]	0.933
Female, n (%)	33 (55.9)	21 (61.8)	0.583
Body mass index, $kg.m^{-2}$	26.7 [23.7, 30.8]	27.2 [24.1, 30.1]	0.854
Education level, n (%)			0.049
Lower (≤ 9 years)	19 (32.2)	18 (52.9)	
Higher (> 9 years)	40 (67.8)	16 (47.1)	
ASA physical status, n (%)			0.277
I—II	35 (59.3)	24 (70.6)	
III	24 (40.7)	10 (29.4)	
Grade of surgery, n (%)			0.912
Minor	15 (25.4)	9 (26.5)	
Intermediate / Major	43 (72.9) / 1 (1.7)	25 (73.5) / 0 (0.0)	

Data are expressed as median [IQR] or number (%). *CDT* Clock Drawing Test, *ASA* American Society of Anesthesiologists

Table 2.3. Baseline and operative characteristics of patients according to their performance at Clock Drawing Test.

Univariable and multivariable logistic regression analyses were performed for the CDT score and other potential confounding variables to evaluate their association with the presence of postoperative decline in olfaction (**Table 2.4.**). After adjustment for age, gender, education level, ASA physical status and grade of surgery, CDT score remained a significant predictor variable. The higher the CDT score was, the lesser were the odds of presenting a postoperative decline in olfactory identification score (OR 0.67, 95% CI 0.48 to 0.94, *P* = 0.022). In the univariable analysis, ASA physical status III was the only other variable to be significantly associated with the presence of postoperative decline in olfaction (OR 3.05, 95% CI 1.08 to 8.59, *P* = 0.035). However, statistical significance was lost in the multivariable model.

Variable	Univariable			Multivariable		
	OR	95% CI	*P* Value	OR	95% CI	*P* Value
CDT score	0.72	0.53–0.99	0.040	0.67	0.48–0.94	0.022
Age	1.03	0.95–1.11	0.472	1.03	0.95–1.12	0.510
Female	0.76	0.28–2.09	0.591	0.86	0.27–2.74	0.803
Lower education level (≤ 9 years)	0.86	0.30–2.42	0.769	0.70	0.22–2.25	0.550
ASA physical status III	3.05	1.08–8.59	0.035	3.21	1.00–10.30	0.051
Intermediate or major surgery	0.70	0.23–2.10	0.520	0.87	0.26–2.89	0.822

OR Odds Ratio, *CI* Confidence Interval, *CDT* Clock Drawing Test, *ASA* American Society of Anesthesiologists

Table 2.4. Univariable and multivariable logistic regression analysis for the prediction of a postoperative decline in olfactory identification score.

We also aimed at analyzing the association between drugs and postoperative decline in olfactory identification score. Overall, median duration of sevoflurane exposure was 146 minutes (ranging from 103 to 213 minutes) and was similar in patients with or without a postoperative decline in olfaction. Sufentanil, ketamine, midazolam and rocuronium doses did not differ between the two groups of patients. On the contrary, median propofol dose (mg/kg) was significantly higher in patients suffering from a postoperative decline in olfactory identification score (2.03 IQR [1.54 to 2.76] vs 1.67 IQR [1.21 to 2.02], *P* = 0.025). Postoperative morphine consumption was not statistically different between both groups.

Discussion

The results of this pilot study in a group of older patients undergoing non-cardiac surgery under general anesthesia with sevoflurane show that 20.4% of patients experience a decline in their olfactory identification function on the first postoperative day compared to their preoperative score. Hernandez et al. analyzed changes in global olfactory function (threshold, discrimination and identification modalities) in the perioperative context in a group of 73 patients [183]. In contrast to our results, they had a worse postoperative global performance of olfactory function in only 5% of their cohort. This difference might be explained partly by the fact that among their 73 patients, only 62 received general anesthesia. Otherwise, their study population was younger (mean age of 51 years old). Interestingly, they observed an overall slight increase in postoperative mean olfactory identification score, which they explained by the known test-retest effect [19]. On the contrary, concerning the postoperative olfactory threshold test, they found that the positive test-retest effect decreased with age. Although we used an olfactory identification test, this age effect could contribute to the greater postoperative decline in our older cohort. Overall, we show a decrease in median olfactory identification score on the first postoperative day, which corroborates existing studies showing similar results either at 3 hours [178,179,180] or, using the discrimination modality, within 15 hours [181] postoperatively. In two of them, olfactory results were retested again at least 3 days postoperatively and came back to baseline [179,180]. In the study from Hernandez and colleagues, postoperative testing occurred later (6 postoperative days on average) and this could have also contributed to the discrepancy of their results [183].

Poor preoperative performance at the CDT was independently associated with immediate postoperative decline in olfactory identification function, even after adjusting for potential confounding variables. Olfactory identification assessment is a quite simple test, which had already been taken the day before the surgery

in our patients, but might still constitute a cognitively demanding task. Of note, it requires both a neurological pathway to “sense” the odor but also higher order cognitive abilities – in particular semantic and executive functions – to identify and eventually name the odor [189,190]. Besides, the results emerging from our primary study showed a clear correlation between preoperative olfactory dysfunction and poor performance at CDT, also supporting the close relationship between olfaction and cognition [184]. Yet, poor performance at CDT before surgery has been shown to increase the risk of developing postoperative delirium [191,192]. The stronger reduction in olfactory identification performance on the day following general anesthesia in poor CDT performers at baseline could thus merely reflect a transient decrease in postoperative cognitive abilities, occurring more often in patients with preoperative altered cognition.

Being classified as ASA physical status III has already been demonstrated to be an independent predictor of postoperative neurocognitive disorder in older patients [148,193,194]. Here, we show an association with worst postoperative olfactory function, though narrowly failing to reach the significance level in the multivariable model, likely because of a lack of power. Therefore, our findings may again support the hypothesis of postoperative olfactory performance being related to postoperative cognitive capacities. Without any pretension to replace a more complete cognitive examination (e.g., the Montreal Cognitive Assessment [160]), olfactory identification testing could potentially constitute a simple and quick clinical bedside tool to assess perioperative cognition.

Not surprisingly, we noted a link between a lower education level and worse performance at CDT. Preoperative cognitive testing is known to be influenced negatively by a low level of education [143], and this was specifically shown for the CDT [195]. Nevertheless, lower education level was not associated with postoperative decline in olfaction and did not seem to affect the association with CDT score in the multivariable analysis.

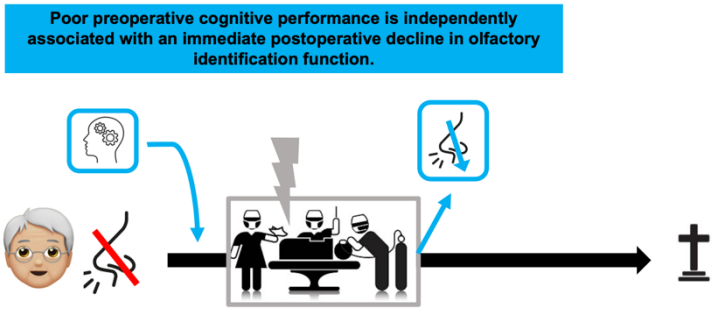
In our study, intraoperative propofol doses were statistically higher in patients with a postoperative decline in olfactory identification function. Propofol has been incriminated in a few case reports as being responsible for postoperative olfactory dysfunction through its activation of gamma-aminobutyric acid type A ($GABA_A$) receptors [176,177], the latter being abundantly found in olfactory-related brain regions [196]. Beside the absence of real evidence supporting this, the difference of less than 0.5mg/kg found between our two groups does not seem clinically significant. As to ketamine, which is thought to influence postoperative cognition [197], the relatively small doses administered in the present cohort did not affect the results. Whether sevoflurane impacts negatively postoperative olfactory function still remains a matter of debate. Our data show that this potential effect, if any, is not related to the duration of exposure.

This study suffers from some limitations. First, this study was exploratory and was a sub-analysis of a larger prospective study, therefore power calculations were not realized specifically for the present aims. In addition, this study was registered retrospectively due to unawareness of registration policy. Second, preoperative cognitive function was evaluated on the sole basis of the CDT [185]. But, despite being neither time nor resource consuming, it does not assess all these cognitive domains with the same precision as a complete neurocognitive battery. Moreover, the method of removing from the total CDT score the 2 points originally allocated for the drawing of the circle has never been validated. Similarly, olfactory testing was limited to the identification modality without including an evaluation of olfactory detection thresholds and discrimination performance. Third, the timing of the postoperative olfactory identification test had a 10-hour range which may have lowered the precision of our observations. Also, performing a second more delayed postoperative assessment of olfaction could have shown whether the observed decline in olfactory identification remained over time. Fourth, pain or anxiety inherent to the upcoming surgery might have had an influence on patients' performance at preoperative testing. Fifth, we did not collect intraoperative burst suppression data and depth of

anesthesia monitoring was not used. This means we did not analyze anesthesia depth and thereby its possible impact on postoperative cognition.

Conclusions

In summary, this pilot study shows a decline in immediate postoperative olfactory identification function in around 20% of older patients scheduled for elective non-cardiac surgery under sevoflurane-based anesthesia. This was associated with poor preoperative performance at the CDT. Whether this decline in postoperative olfaction may be related to poor postoperative cognitive abilities and whether it may persist over time deserve future attention. Larger prospective studies with more comprehensive perioperative cognitive and olfactory testing should bring more insights to these preliminary data.



Graphical summary of the main findings from Chapter 2.

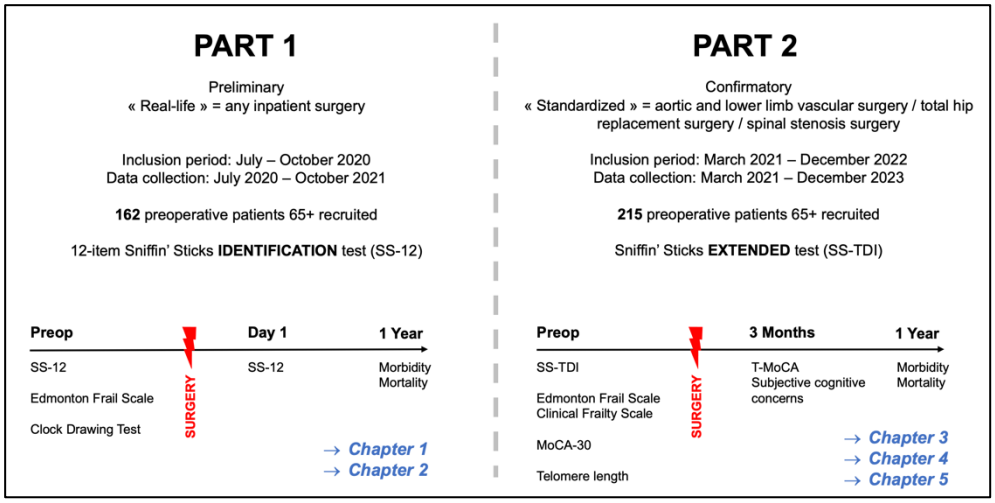
PART 2 – Confirmatory study in standardized groups of older patients undergoing three types of inpatient surgeries

Foreword

The second part of the project consisted of an extensive study following a more comprehensive protocol. In particular, the preoperative testing session intended to assess olfactory function, frailty status, and cognitive function more profoundly. The recruitment phase started in March 2021 and lasted nearly two years. We enrolled a total of 215 older patients scheduled for three selected types of elective surgery: aortic and lower limb vascular surgery, total hip replacement surgery, and lumbar spinal stenosis surgery. By restricting the surgeries, we aimed to have standardized study groups containing a certain kind of population undergoing surgery with its specific postoperative course.

In this study, we evaluated the three modalities of olfaction, hoping to get the most out of this neurologic function. Indeed, we only tested identification in our first trial [184], which was also the case in most of the previously published studies [12]. In addition to the Edmonton Frail Scale test, we decided to use the Clinical Frailty Scale to investigate frailty in our cohort. Given its feasibility and proven association with postsurgical mortality, this second tool recently gained more popularity in perioperative medicine [128]. Therefore, one of the objectives of Chapter 3 was to explore deeper and validate this strong relationship we had previously demonstrated between olfaction and frailty. More importantly, we aimed to examine preoperative olfactory dysfunction's potential to predict postoperative complications and, furthermore, to compare it to frailty's predictive ability. Since one-year data collection is not yet completed, the data presented in this chapter are still preliminary.

Olfactory and cognitive functions are undeniably linked to each other and are both likely to be affected by aging. Perioperative neurocognitive disorders are associated with a higher incidence of morbidity and mortality, which makes their prevention, diagnosis, and management of utmost importance for older patients needing surgery [149]. Yet, frailty and preoperative cognitive dysfunction are thought to be risk factors for developing postoperative neurocognitive disorder (PND) [160][198]. In this larger study, we obtained a more extensive cognitive assessment by administering the Montreal Cognitive Assessment (MoCA) in the preoperative period but also three months after surgery. We also insisted on asking the patients about the subjective complaints they might have experienced in the postoperative period. Our objective in Chapter 4 was to investigate whether preoperative olfactory function predicts PND in cognitively healthy older patients.



Comparative table between Part 1 and Part 2 protocols.

Methods

Study population and protocol

This prospective observational study was approved by the Institutional Ethics Committee of Cliniques universitaires Saint-Luc, Université catholique de Louvain, Brussels, Belgium, on March 3rd, 2020. The study protocol was registered on https://clinicaltrials.gov/study/NCT04761458 in February 2021. This study started in March 2021 and was conducted at the Cliniques universitaires Saint-Luc. Written informed consent was obtained for all patients.

We enrolled patients aged 65 and older scheduled for three types of elective surgery under general anesthesia: aortic and lower limb vascular surgery, total hip replacement surgery, or lumbar spinal stenosis surgery. The exclusion criteria were patients with a history of neurologic disorder (including any type of diagnosed dementia or cognitive impairment), psychiatric disease, severe head trauma, sino-nasal disease or surgery, and any diagnosed olfactory loss. History of COVID-19 was not an exclusion criterion, but patients with a recent COVID-19 infection (< 3 months) or subjective residual olfactory dysfunction were excluded.

The patients underwent a testing session the day before the surgery, covering olfactory, cognitive, and frailty assessments. All surgeries were realized under general anesthesia. The choice of induction and maintenance agents was left to the anesthesiologist in charge.

Olfactory function assessment

We used the Sniffin' Sticks extended test (Burghart Messtechnik GmbH, Wedel, Germany) to evaluate the olfactory function of the preoperative patients. This psychophysical test is a routinely used validated method and consists of three subtests using pen-like odor dispensing devices [19]. The examiner places the

sticks approximately 2 cm in front of the nostrils. First, the odor threshold for n-butanol was assessed using a single-staircase, three alternative forced choice procedure. Triplets of sticks were presented to the patients, with two non-odorant sticks and one stick impregnated with n-butanol. Then, odor discrimination was evaluated also with a three alternative forced choice procedure (using two sticks containing the same odorant and one with a distinct odorant). Odor identification was tested for 16 common odors using a multiple-choice identification from lists of four descriptors each. Each subtest was scored on a maximum of 16 points, with higher scores indicating a higher olfactory function. To quantify global olfactory function, results from the three subtests were put together to form a composite 'TDI score' (48 points), which was the sum of the threshold score T (16 points), the discrimination score D (16 points), and the identification score I (16 points). The original cut-off for normosmia, regardless of age and sex, is defined as a TDI score > 30.5/48.

We also classified olfactory scores into seven percentiles categories according to recently updated age- and sex-adjusted norms of the Sniffin' Sticks tests [24]. In some analyses, the patients were separated into two groups, having either a TDI, threshold, discrimination, or identification score $\leq$ the 25th percentile (p25) or > p25.

Cognitive function evaluation

All patients underwent the French version of the Montreal Cognitive Assessment (MoCA) as a preoperative cognitive screening test on the day before surgery. The complete version of this test has a best maximum score of 30 points (MoCA-30) and has been validated as a screening instrument for mild cognitive impairment [151].

Postoperative cognitive evaluation was realized 12 weeks after the surgery during a telephone interview. The patients were first asked about subjective

cognitive concerns (SCC), consisting of seven yes/no questions about a recent change in the following items: memory; remembering a short list, things from one second to the next, recent events; difficulties with understanding or following spoken instructions, a group conversation or the plot of a television program; and trouble finding one's way in familiar streets. These simple SCC were shown to be associated with further change in episodic memory in a large study involving older women [199]. Then, we administered the telephone version of the MoCA (T-MoCA) with a maximum total score of 22 points. This test is a simplified version of the MoCA-30, obtained by removing items that require visual stimuli or pencil and paper [200]. It has also been validated in regard to mild cognitive impairment screening. To accurately compare pre- and postoperative MoCA testing, we computed a preoperative MoCA-22 score corresponding to the items evaluated in the T-MoCA. Objective cognitive decline was established as a decrease of at least one standard deviation in the T-MoCA (corresponding to a decrease of at least 3 points).

We defined postoperative neurocognitive disorder (PND) as the presence of one or more SCC and/or an objective cognitive decline.

Frailty assessment

We used two different tests to identify the level of frailty in our study population: the Edmonton Frail Scale (EFS) and the Clinical Frailty Scale (CFS) (see Section 1, Chapter 4 for more details on methodology). Both tests are strongly recommended in the perioperative setting [128]. We defined frailty as scoring ≥6/17 at the EFS. The CFS is a fast and intuitive tool based on our clinical appreciation of the patient in front of us [134]. It has a maximum score of 7 points, and we settled the cut-off for frailty as of the "Apparently vulnerable" category (4 points).

Postoperative morbidity and mortality

We obtained postoperative data using local hospital medical records and the Belgian Health network (provided that the patients had authorized access), which allowed us to get an overall view of the patient's medical information. We used the Clavien-Dindo classification to grade postoperative complications within one year after elective surgery [141]. We only collected moderate to severe complications (grade 2 to 4) and mortality (grade 5), and we did not consider minor complications (grade 1). Given the low mortality rate, we gathered postoperative complications (grades 2 to 4) and mortality (grade 5) into one "postoperative morbidity/mortality" group in our analyses.

Covariables

We collected the following demographic data: age, sex, BMI, and level of education. Anxiety and depression symptoms were measured through the Hospital Anxiety and Depression Scale (HADS), which provides two different scores: an anxiety score and a depression score [201]. All the patients had a blood sample taken for Apolipoprotein E (ApoE) genotyping. Other medical information that was gathered comprised smoking status, American Society of Anesthesiologists (ASA) physical status, Charlson Comorbidity Index (CC Index), and duration of anesthesia (from induction of anesthesia until tracheal extubation).

Statistical analysis

The primary outcome was the incidence of postoperative morbidity and mortality. The secondary outcome was the prevalence of postoperative neurocognitive disorder according to preoperative olfactory function.

Existing studies on olfaction and mortality reported very few details about their statistical results. We used the mortality data shown in the study of Pinto et al. in 2014 [61] (which gave the greatest number of statistical information) and a 12% anosmia frequency reported in the population aged 65 years old and more [50] for power analysis. Using G*Power 3.1 – U Düsseldorf with alpha error 0.05 / power 0.80, the sample size needed was 252. Yet, similar data on perioperative outcome regarding olfactory function have never been reported. Thus, we set the sample size at a minimum of 200 patients to achieve statistical significance for the primary outcome. Since the sample size was not calculated specifically regarding the secondary outcome (PND), we realized a sensitivity power analysis to check for the reliability of our findings, also using G*Power 3.1 – U Düsseldorf. We compared (1) the Cramér's V value of the chi square analysis of the incidence of PND according to the preoperative TDI score (≤p25 or >p25) to (2) the minimal detectable effect size W computed using G*Power 3.1 – U Düsseldorf with alpha error 0.05 / power 0.80 / sample size 139 / degree of freedom 1.

We analyzed the data using SPSS version 28.0. We used the Kolmogorov-Smirnov test to evaluate the normality of the data. Continuous variables were not normally distributed and were presented as medians (interquartile range). Ordinal variables were reported as medians (interquartile range). Comparisons between groups of patients were realized with a Pearson χ^2 for nominal variables and with a Mann-Whitney U-test or a Kruskal-Wallis test for continuous variables. We performed univariable and multivariable linear regression analyses to associate olfactory scores with the EFS score. We used univariable and multivariable binary logistic regression analyses to predict postoperative morbidity/mortality and postoperative neurocognitive disorder. For regression analyses, we adjusted for potential confounding variables related to olfactory function (age, gender) or to the outcome variable. Any *P*-value < 0.05 was considered significant.

Chapter 3. The intricate links between preoperative global olfactory dysfunction, frailty, and prediction of postoperative morbidity and mortality in older surgical patients: preliminary results

As data collection is still ongoing,
this chapter presents and discusses only intermediate analyses.

Results

Up to now, we have been able to collect data for 185 patients, as shown in **Figure 2.7**. We compared baseline and operative characteristics for these patients according to their preoperative olfactory function (**Table 2.5.**). MoCA-30 scores were slightly lower in the group with a TDI score ≤p25 (*P* = 0.035). We did not find any other statistically significant difference between both groups.

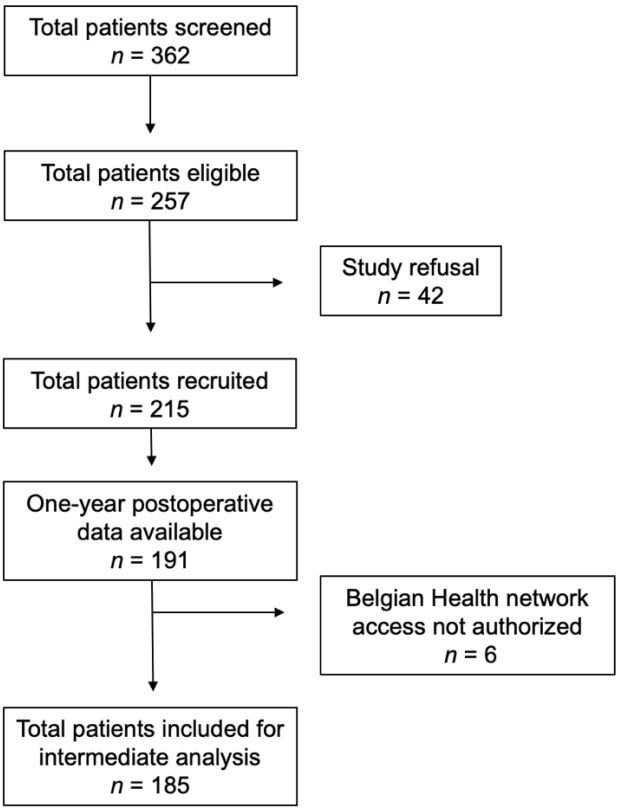


Figure 2.7. Study flowchart.

Characteristics	TDI score ≤p25 n = 66	TDI score >p25 n = 119	*P*-value
Age, year	72 [68-76]	74 [70-78]	0.078
Female, n (%)	33 (50.0%)	71 (59.7%)	0.20
Body mass index, $kg.m^{-2}$	27.7 [24.1-33.4]	27.3 [23.8-30.5]	0.20
Smoking status - Present smoker - Former smoker - Non-smoker	 9 (13.6%) 25 (37.9%) 32 (48.5%)	 15 (12.6%) 33 (27.7%) 71 (59.7%)	0.30
History of COVID-19, n (%)	10 (15.2%)	16 (13.4%)	0.75
ASA physical status III-IV, n (%)	30 (45.5%)	53 (44.5%)	0.90
Charlson Comorbidity Index	1 [0-3]	1 (0-2)	0.21
Preoperative MoCA-30	24 [22-27]	25 [23-27]	0.035
HADS - depression score	5 [2-7]	4 [2-6]	0.095
Type of surgery - Aortic or lower limb revascularization surgery - Total hip arthroplasty - Spinal stenosis surgery	 18 (27.3) 23 (34.8) 25 (37.9)	 21 (17.6) 58 (48.7) 40 (33.6)	0.14
Duration of anesthesia, min	165 [122-241]	137 [122-241]	0.065

Data are expressed as median [IQR] or number (%). TDI score: Threshold Discrimination Identification score, ASA: American Society of Anesthesiologists, MoCA: Montreal Cognitive Assessment, HADS: Hospital Depression and Anxiety Scale

Table 2.5. Baseline and operative characteristics according to preoperative olfactory function.

OLFACTION AND FRAILTY

As shown in **Table 2.6.**, we found differences in the EFS (*P* = 0.037) and the CFS (*P* = 0.002) scores depending on whether the patients had a preoperative TDI score ≤p25 or >p25. In the group with a TDI score ≤p25, patients labeled as frail with the EFS or the CFS were more frequent, but this difference was not statistically different.

When we investigated the patients having a TDI score > 30.5 (original cut-off for normosmia regardless of age and sex), only 4.3% (2/47) had an EFS score ≥6/17

against 30.4% (42/138) of the patients with a TDI score ≤ 30.5 (p < 0.001). The median age was 72 (68-77) in the group with a TDI score > 30.5 and 74 (70-78) in the group with a TDI score ≤ 30.5 (*P* = 0.051).

Frailty variable	**Overall patients n = 185**	**TDI score ≤p25 n = 66**	**TDI score >p25 n = 119**	***P*-value**
EFS score	3 [2-5]	4 [2-6]	3 [2-5]	0.037
CFS score	3 [2-3]	3 [3-4]	3 [2-3]	0.002
Patients with an EFS score ≥ 6/17, %	44 (23.8)	18 (27.3)	26 (21.8)	0.40
Patients with a CFS score ≥ 4/7, %	44 (23.8)	21 (31.8)	23 (19.3)	0.056

Data are expressed as median [IQR] or number (%). TDI score: Threshold Discrimination Identification score, EFS: Edmonton Frail Scale, CFS: Clinical Frailty Scale

Table 2.6. Edmonton Frail Scale and Clinical Frailty Scale results according to their preoperative global olfactory function (TDI score percentile for age and gender)

When assigning the patients into two groups, robust/frail, according to the EFS or the CFS score, we observed lower TDI scores in the frail patients (*P* < 0.001) (**Figure 2.8.**). This was also the case concerning the threshold, the discrimination, and the identification scores (all *P*-values < 0.05).

In univariable linear regression analyses, we found the EFS score to be significantly associated with preoperative olfactory threshold, discrimination, and identification scores (all *P*-values < 0.001) (**Table 2.7.**). Despite gender not being associated with the EFS score, we included it in the multivariable models given its relationship with olfactory scores. After adjustment for age, sex, and Charlson Comorbidity Index, the three olfactory scores remained significantly correlated with the EFS score (**Table 2.8.**).

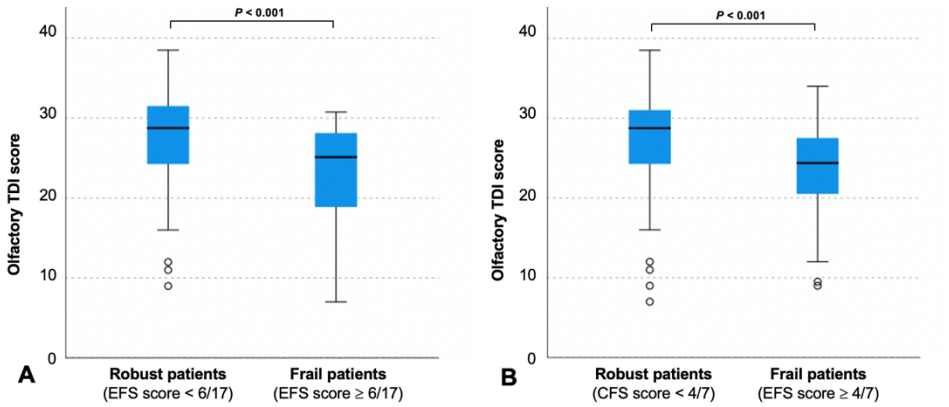


Figure 2.8. Olfactory TDI score according to frailty status, based on the Edmonton Frail Scale (**A**) and the Clinical Frailty Scale (**B**). TDI: Threshold, Discrimination, Identification, EFS: Edmonton Frail Scale, CFS: Clinical Frailty Scale.

Variable	Standardized regression coefficient	*P*-value
Preoperative olfactory threshold score	- 0.289	< 0.001
Preoperative olfactory discrimination score	- 0.277	< 0.001
Preoperative olfactory identification score	- 0.309	< 0.001
Age	0.162	0.028
Female sex	- 0.034	0.641
Charlson Comorbidity Index	0.447	< 0.001

Table 2.7. Univariable linear regression analysis associating olfactory scores and other variables with the EFS score.

Variable	Standardized regression coefficient	*P*-value
Preoperative olfactory threshold score	- 0.242	< 0.001
Age	0.113	0.074
Female sex	- 0.213	0.002
Charlson Comorbidity Index	0.493	< 0.001
Preoperative olfactory discrimination score	- 0.219	0.001
Age	0.093	0.15
Female sex	- 0.231	< 0.001
Charlson Comorbidity Index	0.490	< 0.001
Preoperative olfactory identification score	- 0.202	0.003
Age	0.115	0.074
Female sex	- 0.220	0.001
Charlson Comorbidity Index	0.461	< 0.001

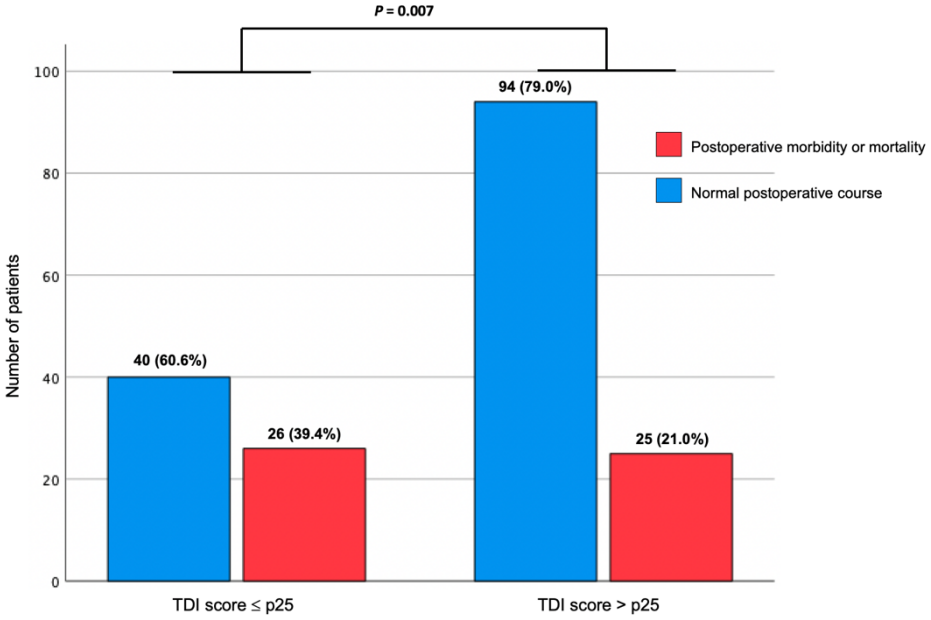
Table 2.8. Multivariable linear regression models for the prediction of the Edmonton Frail Scale score.

OLFACTION AND POSTOPERATIVE MORBIDITY AND MORTALITY

Within one year after surgery, 48 (26.0%) patients developed a postoperative complication, and 3 (1.6%) patients died. 39.4% of the patients with a preoperative TDI score ≤p25 suffered from postoperative morbidity/mortality against only 21.0% of the patients with a TDI score >p25 ($P = 0.007$). The results are shown in **Figure 2.9.** On the other hand, when we isolated patients with a TDI score > 30.5 (i.e., the original cut-off for normosmia, without considering age or sex norms), we noticed that only 10.6% of these patients (5/47) would develop postoperative morbidity/mortality compared to the rest of the cohort ($P = 0.003$). In contrast, the incidence was of 32.0% (40/125) in the hyposmic population (i.e.,

a TDI score ≤ 30.5 and ≥ 16.5) and 46.2% (6/13) among the anosmics (i.e., a TDI score < 16.5).

Figure 2.9. One-year postoperative morbidity/mortality according to preoperative olfactory TDI score.



We performed univariable and multivariable logistic regression models predicting one-year postoperative morbidity/mortality in our cohort according to the preoperative olfactory threshold, discrimination, and identification scores (**Tables 2.9. and 2.10.**).

Variable	OR	95% CI	*P*-value
Preoperative olfactory threshold score (T)	0.83	0.71-0.97	0.018
Preoperative olfactory discrimination score (D)	0.78	0.68-0.89	< 0.001
Preoperative olfactory identification score (I)	0.82	0.73-0.92	< 0.001
Age	0.99	0.94-1.05	0.74
Female sex	0.30	0.16-0.60	< 0.001
Charlson Comorbidity Index	1.38	1.16-1.65	< 0.001
Aortic or lower limb revascularization surgery	4.51	2.14-9.52	< 0.001
Duration of anesthesia	1.01	1.00-1.01	0.008
Preoperative MoCA-30	0.90	0.81-0.99	0.032
HADS - depression score	1.09	0.99-1.21	0.097

HADS: Hospital Anxiety and Depression Scale, MoCA: Montreal Cognitive Assessment.

Table 2.9. Univariable logistic regression analysis for the prediction of postoperative morbidity/mortality.

Model 1 accounted for age and sex, given their relationship with olfactory scores, and was automatically added to every other model. In Model 2, adjusting for comorbidities, only the discrimination and the identification scores remained predictive. The Charlson Comorbidity Index was significantly associated with the outcome variable in all models (T-Model 2: $P = 0.010$, D-Model 2: $P = 0.015$, I-Model 2: $P = 0.035$). Model 3 adjusted for type of surgery and duration of anesthesia. Similarly to Model 2, only the discrimination and the identification scores were statistically associated with postoperative morbidity/mortality. Aortic or lower limb revascularization surgery was associated with the outcome variable in the T-Model 3 ($P = 0.017$) and the D-Model 3 ($P = 0.037$), but not in the I-Model 3 ($P = 0.058$). Duration of anesthesia lost statistical significance in the multivariable models. In Model 4, when accounting for preoperative cognition, the olfactory discrimination and identification scores were still predictive of postoperative morbidity/mortality, contrary to the threshold score. In the T-Model 4, the MoCA-30 score was statistically correlated to the outcome variable ($P = 0.041$), which was not the case in the D-Model 4 and the I-Model 4 (p-values > 0.1). Adding the EFS score to the models had a significant effect on

the three olfactory scores, and the EFS score remained statistically significantly correlated to postoperative morbidity/mortality. The threshold and nearly the identification scores lost their association with the outcome variable. In D-Model 5, the effect of the discrimination score was decreased but still significantly associated with postoperative morbidity/mortality (P = 0.010). Model 6 took into consideration the HADS-depression score, which itself was not correlated with the outcome variable in multivariable analyses. In the T-Model 6, the D-Model 6, and the I-Model 6, the olfactory scores were all significantly associated with postoperative morbidity/mortality with an attenuated effect, especially for the identification score.

We compared the metrics of the EFS, the CFS, the olfactory TDI scores, or their combination in their ability to predict postoperative morbidity/mortality in our study population (**Table 2.11.**). In particular, we noticed a higher sensitivity of the TDI score ≤p25 (51.0%) compared to an EFS score ≥6/17 (39.2%). Being tested "positive" to either one of these tests increased sensitivity to 70.6% and resulted in a negative predictive value of 83.9%. The highest positive predictive value (55.6%) was obtained when combining the presence of a TDI score ≤p25 and an EFS score ≥6/17, but then the sensitivity was very low. The combination of a TDI score ≤30.5 and an EFS score ≥6/17 also showed a higher positive predictive value but this time with a higher sensitivity. Overall, a CFS score ≥4/7 was less performant. A TDI score ≤30.5 had a sensitivity of 90.2% and a negative predictive value of 89.4%.

Variable	OR	95% CI	*P*-value
Preoperative olfactory threshold score (T)	0.83	0.71-0.97	0.018
T - Model 1: age, sex	0.84	0.71-0.99	0.033
T - Model 2: Model 1, Charlson Comorbidity Index	0.85	0.72-1.01	0.060
T - Model 3: Model 1, aortic or lower limb revascularization surgery, duration of anesthesia	0.85	0.71-1.00	0.056
T - Model 4: Model 1, MoCA-30	0.85	0.72-1.01	0.060
T - Model 5: Model 1, EFS score	0.90	0.75-1.07	0.22
T - Model 6: Model 1, HADS - depression score	0.84	0.71-0.99	0.043
Preoperative olfactory discrimination score (D)	0.78	0.68-0.89	< 0.001
D - Model 1: age, sex	0.79	0.68-0.91	0.001
D - Model 2: Model 1, Charlson Comorbidity Index	0.80	0.68-0.93	0.004
D - Model 3: Model 1, aortic or lower limb revascularization surgery, duration of anesthesia	0.81	0.70-0.94	0.007
D - Model 4: Model 1, MoCA-30	0.81	0.69-0.95	0.009
D - Model 5: Model 1, EFS score	0.82	0.70-0.95	0.010
D - Model 6: Model 1, HADS - depression score	0.79	0.68-0.92	0.002
Preoperative olfactory identification score (I)	0.82	0.73-0.92	< 0.001
I - Model 1: age, sex	0.84	0.74-0.95	0.004
I - Model 2: Model 1, Charlson Comorbidity Index	0.86	0.76-0.98	0.021
I - Model 3: Model 1, aortic or lower limb revascularization surgery, duration of anesthesia	0.85	0.75-0.97	0.013
I - Model 4: Model 1, MoCA-30	0.86	0.76-0.98	0.021
I - Model 5: Model 1, EFS score	0.88	0.77-0.99	0.043
I - Model 6: Model 1, HADS - depression score	0.85	0.75-0.96	0.007

MoCA: Montreal Cognitive Assessment, EFS: Edmonton Frail Scale, HADS: Hospital Anxiety and Depression Scale.

Table 2.10. Odds ratios and 95% confidence intervals of the preoperative olfactory scores in logistic regression models predicting postoperative morbidity/mortality.

Test and cut-off used	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
EFS score ≥6/17	39.2	82.1	45.5	78.0
CFS score ≥4/7	35.3	80.6	40.9	76.6
TDI score ≤p25	51.0	70.1	39.4	79.0
TDI score ≤p25 and/or EFS score ≥6/17	70.6	58.2	39.1	83.9
TDI score ≤p25 and EFS score ≥6/17	19.6	94.0	55.6	75.4
TDI score ≤30.5	90.2	31.3	33.3	89.4
TDI score ≤30.5 and/or EFS score ≥6/17	90.2	29.9	32.9	88.9
TDI score ≤30.5 and EFS score ≥6/17	39.2	83.6	47.6	78.3

EFS: Edmonton Frail Scale, CFS: Clinical Frailty Scale, TDI: Threshold, Discrimination, Identification

Table 2.11. Detailed metrics for preoperative tests used to predict postoperative morbidity/mortality in the entire study population.

As we recruited patients scheduled for either orthopedic surgery (total hip arthroplasty or spinal stenosis surgery) or vascular surgery (aortic or lower limb revascularization surgery), we aimed to compare them in terms of olfactory function, frailty, and postoperative morbidity/mortality. The vascular patients were more frequently categorized as hyposmic or anosmic than as normosmic compared to the orthopedic patients (P = 0.029 and P = 0.004, respectively, **Figure 2.10.**). 46.2% (18/39) of the vascular patients had a TDI score ≤p25 compared to 32.9% (48/146) among the orthopedic subgroup, but the difference was not statistically significant. We found an EFS score ≥6/17 in 48.7% (19/39) of the patients undergoing vascular surgery compared to only 17.1% (25/146) in the rest of the cohort (P < 0.001).

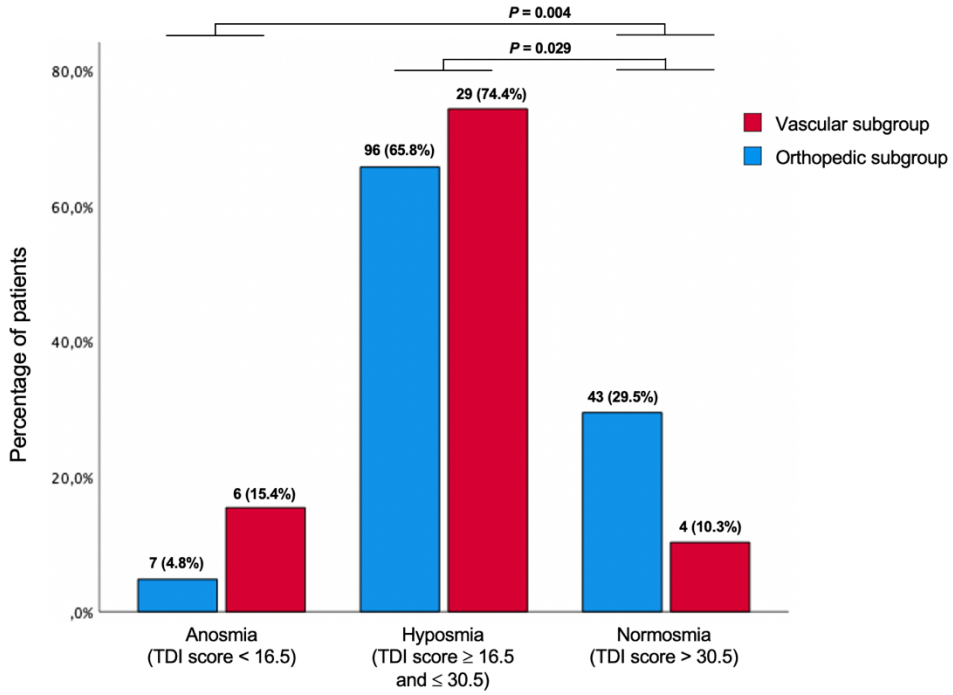


Figure 2.10. Olfactory function of the patients according to the surgery subgroup – vascular or othopedic. TDI: Threshold, Discrimination and Identidication.

Given the major differences between these two subgroups, we also analyzed separately the metrics of the EFS score and the olfactory scores. Postoperative morbidity/mortality occurred in 53.8% (21/39) of the vascular patients. We calculated better metrics when using a TDI score ≤p25 than the EFS score in this subgroup (**Table 2.12.**). Combining the presence of a TDI score ≤p25 and an EFS score ≥6/17 did not add much than the use of the TDI score ≤p25 alone in terms of positive predictive value (80.0% vs 77.8%). We did not analyze in detail the TDI score cut-off of ≤30.5 since only 4 patients (10.3%) had a TDI score above this limit in this specific group. As for the orthopedic subgroup, only 20.5% (30/146) suffered from postoperative morbidity/mortality. Here, we calculated better metrics with the EFS score than by using a TDI score ≤p25 (**Table 2.13.**). All the tests had rather low positive predictive values. When

combining the presence of a TDI score ≤30.5 and of an EFS score ≥6/17, we found the highest positive predictive value. The highest negative predictive value was obtained with the TDI score ≤30.5.

Test and cut-off used	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
EFS score ≥6/17	52.4	55.6	57.9	42.1
TDI score ≤p25	66.7	77.8	77.8	66.7
TDI score ≤p25 and/or EFS score ≥6/17	81.0	44.4	63.0	66.7
TDI score ≤p25 and EFS score ≥6/17	38.1	88.9	80.0	55.2
TDI score ≤30.5	95.2	16.7	57.1	75.0

EFS: Edmonton Frail Scale, CFS: Clinical Frailty Scale, TDI: Threshold, Discrimination, Identification

Table 2.12. Detailed metrics for preoperative tests used to predict postoperative morbidity/mortality in the vascular patients.

Test and cut-off used	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
EFS score ≥6/17	30.0	86.2	36.0	82.6
TDI score ≤p25	40.0	69.0	25.0	81.6
TDI score ≤p25 and/or EFS score ≥6/17	63.3	60.3	29.2	86.4
TDI score ≤p25 and EFS score ≥6/17	6.7	94.8	25.0	79.7
TDI score ≤30.5	86.7	33.6	25.2	90.7
TDI score ≤30.5 and/or EFS score ≥6/17	86.7	31.9	24.8	90.2
TDI score ≤30.5 and EFS score ≥6/17	30.0	87.9	39.1	82.9

EFS: Edmonton Frail Scale, CFS: Clinical Frailty Scale, TDI: Threshold, Discrimination, Identification

Table 2.13. Detailed metrics for preoperative tests used to predict postoperative morbidity/mortality in the orthopedic patients.

Discussion

In this more extensive prospective observational study, we obtained encouraging preliminary results. They confirm our previously published results and bring new strong evidence regarding the links between preoperative olfaction, frailty, and postoperative morbidity in a population of older patients undergoing elective non-cardiac surgery.

OLFACTION AND FRAILTY

The present results showed a clear correlation between olfactory function and two widely used preoperative frailty tests, the EFS and the CFS [128]. In 2020, a systematic review including three studies, of which only one had assessed olfaction with a psychophysical test, could not conclude, given too sparse evidence [163][104]. Since then, five papers have reported a significant correlation between semi-objective testing of olfactory identification dysfunction and frailty [162][202][203][204], including our previous work [184]. Two other studies showed a link using subjective evaluation of olfaction [205][206].

What is interesting is the diversity of the frailty tests that correlated with olfactory identification dysfunction: handgrip strength measurement [104][202], the appendicular skeletal muscle mass index [104], the 37- or 39-item Frailty Index [162][203], the Risk Analysis Index [204], the CFS [184], and the EFS [184]. Together, these tests capture a broad spectrum of frailty, going from the physical frailty phenotype model to the accumulation of deficits model – typically represented by the frailty index [207]. Of note, Xue's team has recently shown a high discrepancy when diagnosing frailty in individuals using either a physical frailty phenotype test or a frailty index [208]. Nagururu and colleagues, who were the first to investigate the olfactory threshold function in addition to the identification function, showed that low performance in both modalities was associated with the physical frailty phenotype [203]. Still, only olfactory identification was correlated to a 37-item frailty index. They explained this

difference by the neurocognitive variables weighting their frailty index, which would probably relate more to olfactory identification than threshold. Therefore, they suggested the role of mediators other than cognitive impairment alone in the association between olfaction and frailty. Besides, they only used six different levels for determining the olfactory threshold, which may account for more limited findings. In contrast, we found a significant association between all three olfactory modalities – threshold, discrimination, and identification – and two frailty tests. The CFS may be more akin to the physical frailty phenotype and, just like the latter, does not include a direct cognitive component. Instead, the EFS is seen as belonging to the accumulation of deficits model but, compared to the frailty index, represents much more than merely an accumulation of medical conditions and has been associated with multi-dimensional geriatric conditions [133]. In the light of existing evidence and of our preliminary data, global olfaction is linked to frailty in plural ways, probably reflecting multifactorial vulnerability.

Age is undeniably associated with more frailty and poorer olfaction [123][209]. Yet, we found olfactory scores to predict frailty even when taking age, sex, and comorbidities into account. This comes as supplementary proof that "age-related" olfactory decline does not simply reflect chronological age and needs to be seen in a broader picture. On the other hand, having a TDI score above 30.5 – i.e., the definition of normosmia, regardless of age and sex – made frailty prevalence drop drastically. This normosmic group's median age was slightly lower, but the difference was not statistically significant. Thus, a good performance at olfactory testing ruled out frailty most of the time.

OLFACTION AND POSTOPERATIVE MORBIDITY AND MORTALITY

These preliminary results provide new data regarding the substantial and dose-dependent link existing between preoperative global olfactory dysfunction and postoperative morbidity and mortality in older surgical patients. Our first study of

155 patients showed that recognizing correctly 6 or fewer odors at a 12-item identification screening test predicted poor 1-year outcome after various elective surgeries [184]. Another study with 165 patients undergoing cardiac surgery found no statistically significant difference in in-hospital postoperative complications and mortality between olfactory-impaired patients and the rest of their cohort. However, they used a higher cut-off for olfactory dysfunction (≤ 8 in a 12-odor identification test) and may have lacked power for this in-hospital outcome, at least concerning mortality, which hit only 8 patients [210]. A recent trial by Mady et al. measured olfactory identification function with a 40-item identification test in 51 individuals requiring head and neck cancer surgery, and they found that severe anosmia was associated with a three-day increased length of stay [204]. Here, we report a nearly two times higher incidence of 1-year postoperative complications in patients with a TDI score below the 25th percentile for age and sex. Besides, when considering the "raw" TDI scores regardless of age and sex, we found a 4-fold difference in the incidence of poor postoperative outcome between normosmic and anosmic groups. Indeed, multivariable analyses confirmed the predictive ability of the olfactory scores irrespective of age and sex. This may be paralleled with our similar data regarding frailty and raises questions about the concept of age-related olfactory decline being a "normal" feature of aging.

This is the first study to investigate the three modalities of olfactory function with postoperative outcome. The discrimination and the identification scores were both independent predictors, even after adjusting for comorbidities, type of surgery (i.e., vascular surgery vs. hip or back surgery) and duration of anesthesia, cognitive function, or depression. This was not the case for the threshold modality, narrowly losing statistical significance in all the regression models except when accounting for depression. Part of the explanation might lie in a lack of power. Nonetheless, this may also illustrate the caricatural dichotomization of peripheral – i.e., the threshold function – and central olfaction – i.e., the discrimination and the identification functions – and everything that

comes along. The predictive ability of the discrimination modality was somewhat higher than that of the identification score. In the age and sex-adjusted model, a 1-point increase in the discrimination score led to a 21% lower probability of developing postoperative morbidity and mortality, whereas the effect was 5% smaller for the identification score. We found no other study investigating the olfactory discrimination score with outcome. Therefore, whether there is a clinical meaning behind this difference will require further research.

Concerning preoperative cognition, the MoCA-30 score remained significantly associated with postoperative morbidity and mortality only in the model analyzing olfactory threshold score. This suggests that the threshold modality might not – sufficiently – reflect the "part" of cognitive dysfunction involved in poor outcome, as opposed to the discrimination and the identification functions. Indeed, the impact of cognition on the threshold modality, though undeniably present, is known to be smaller than on the other two modalities [189][211]. We may also draw from these models that cognition may be responsible for some, but not all, of the underlying mechanisms linking preoperative olfactory dysfunction to postoperative complications. If we leave the specific perioperative context, this is consistent with the data from a recent meta-analysis showing that olfactory dysfunction was associated with significantly higher all-cause mortality while accounting for cognitive function [212]. The study from Liu and colleagues, included in this meta-analysis, had found neurodegenerative diseases to explain 22% of the higher 10-year mortality found in olfactory-impaired individuals [65].

Interestingly, accounting for comorbidities or for vascular surgery – clustering very ill patients and associated with higher morbidity and mortality in the postoperative course – had a relatively small effect on the association of the discrimination or the identification functions with postoperative morbidity and mortality. These results corroborate our previous data [184], as well as those from the studies investigating olfactory dysfunction and general mortality, of which most had included cardiovascular disease in their analyses [12][213].

Medical comorbidities cannot be neglected when assessing an older surgical patient and obviously constitute a risk factor for developing postoperative complications and death. Still, they do not seem to mediate much of the relationship between preoperative olfaction and postoperative outcome.

While knowing that olfactory function and frailty are strongly linked [212], we purposely added the EFS score to our models to confirm our previous results [184]. This had the largest impact on the models, showing an essential role of frailty as an underlying mechanism in the relationship between olfactory dysfunction and poor postoperative outcome. In the present trial, however, the discrimination score remained predictive, as did the identification score, though the latter barely reached statistical significance. Preoperative olfactory dysfunction would thus remain, at least partly, a predictor of postoperative complications, independently from frailty. Nevertheless, we must bring some nuance in that frailty is complex, and the EFS may not cover all its facets [208].

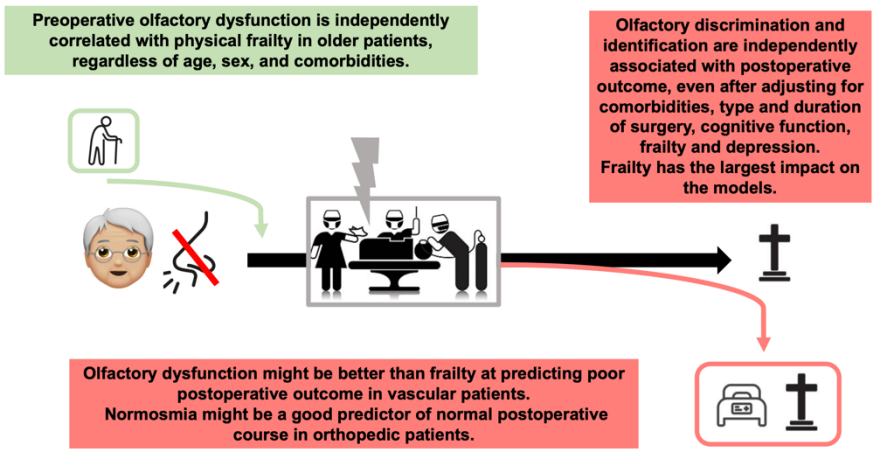
The association between olfactory dysfunction and postoperative outcome was found to be weakened in patients with depressive symptoms. This is in line with some studies linking olfactory dysfunction and mortality, while others did not observe a decreased effect with depression [59][212].

Our following approach was more pragmatic since we compared the concrete predictive ability of both preoperative testing, separately and combined, in our study sample. With no surprise, the incidence of postoperative morbidity and mortality was much higher in the vascular patients, concerning 53.8% of them in contrast to only 20.5% of the orthopedic subgroup individuals. Also, the prevalence of frailty and olfactory dysfunction was higher in vascular individuals. Consequently, the tests did not have the same impact in these two different surgical subgroups. Interestingly, in the vascular subgroup, having a TDI score $\leq$p25 constituted the more efficient test with a positive predictive value of 77.8%. Against all expectations, adding the EFS seemed paradoxically

counterproductive. Indeed, this decreased either sensitivity or specificity while not doing better in terms of predictive values. On the contrary, in orthopedic patients, a TDI score ≤p25 was overall less performant than the EFS score. The use of both a TDI score ≤30.5 and an EFS score ≥6/17 was only slightly better than using the EFS alone. But, more importantly, our analyses highlighted the relatively small predictive power of both preoperative frailty and olfactory dysfunction in a sample with a lower prevalence of poor postoperative outcome. The TDI normosmia cut-off of 30.5 made no sense in vascular patients since it concerned only 10.3% of them. On the other hand, it provided an extremely high negative predictive value (90.7%) in the orthopedic subgroup, which would then bring the safety of not missing a patient who will develop a postoperative complication. Most studies demonstrating the efficacy of frailty assessment in predicting postoperative complications only used regression analyses [214][215][138]. Our findings indicate the need for deepened analysis to derive more accurate information on the true predictive power and avoid any misconception in the interpretation of preoperative screening tests [216]. This issue has also been recently raised by Sonny et al., who demonstrated a very poor discriminative ability in two preoperative frailty tests [217].

Limitations

It should be recalled that these results are preliminary and will require complete data to draw final conclusions. Here, we used only the MoCA test to represent preoperative cognition, which remains a screening test and may not have the same accuracy as a complete neurocognitive battery. Similarly, the EFS and the CFS are often used perioperatively as screening tests for frailty, but a large panel of more exhaustive geriatric assessments exists. We had a low rate of postoperative death, which precluded any specific analysis for this outcome. Lastly, the vascular subgroup was much smaller than the orthopedic subgroup, and this may have influenced our analyses.



Graphical summary of the main findings from Chapter 3.

Chapter 4. Olfactory dysfunction predicts postoperative neurocognitive disorder in older cognitively healthy individuals scheduled for elective non-cardiac surgery

For this secondary outcome, data has been fully collected.
This chapter presents and discusses the final analyses.

Results

In this secondary analysis, we finally included 140 patients (see flowchart in **Figure 2.11.**). As the outcome is postoperative neurocognitive disorder, suffering from preoperative baseline cognitive impairment was an exclusion criterion. Originally, the cut-off score for detecting mild cognitive impairment was <26/30. We used the lowered cut-off of <23/30 proposed by Thomann and colleagues in 2020 to increase specificity. We therefore excluded from the analysis the patients obtaining a preoperative MoCA-30 score ≤ 22.

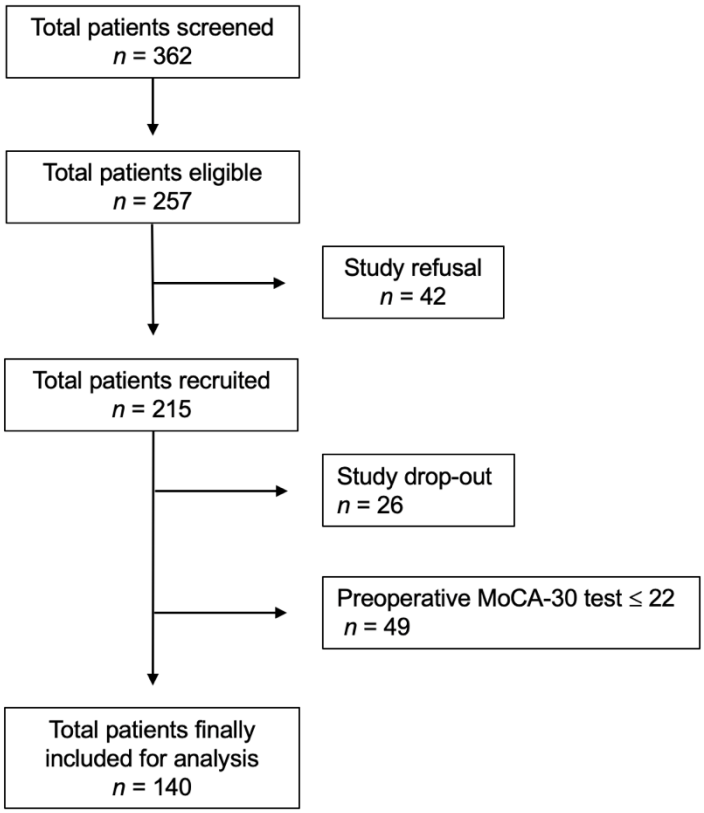


Figure 2.11. Study flowchart.

Table 2.14. shows the baseline and operative characteristics of the study population according to their preoperative olfactory function. The HADS-depression score was higher in the patients with a TDI score ≤p25 (*P* = 0.05). None of the other variables differed significantly between the two groups.

Characteristics	TDI score ≤p25 n = 39	TDI score >p25 n = 101	*P*-value
Age, year	70 [68-78]	74 [69-78]	0.17
Female, n (%)	21 (53.8)	56 (55.4%)	0.87
Body mass index, $kg.m^{-2}$	27.2 [22.7-33.3]	27.7 (24.4-30.5)	0.91
Lower level of education (≤ 9 years), n (%)	9 (23.1)	15 (14.9)	0.25
History of COVID-19, n (%)	7 (17.9)	14 (13.9)	0.54
Hospital Anxiety and Depression Scale (HADS)			
- Anxiety score	7 [5-10]	6 [4-9]	0.39
- Depression score	5 [3-7]	4 [2-6]	0.050
ASA physical status III-IV, n (%)	15 (38.5)	43 (42.6)	0.66
ApoE ε4 carrier, n (%)	10/37 (27.0)	22/95 (23.2)	0.64
Type of surgery			0.80
- Aortic or lower limb revascularization surgery	9 (23.1)	19 (18.8)	
- Total hip arthroplasty	16 (41.0)	47 (46.5)	
- Spinal stenosis surgery	14 (35.9)	35 (34.7)	
Duration of anesthesia, min	148 [116-244]	136[(96-200]	0.33
Use of pre- or intraoperative benzodiazepine, n (%)	10 (25.6)	24 (23.8)	0.82
Sufentanil total dose, $mcg.kg^{-1}$	0.14 [0.10-0.21]	0.14 [0.09-0.17]	0.57
Propofol total dose, $mg.kg^{-1}$	1.74 [1.19-2.25]	1.77 [1.08-2.24]	0.55
Ketamine total dose, $mg.kg^{-1}$	0.47 [0.42-0.63]	0.48 [0.39-0.54]	0.88
Sevoflurane-based GA, n %)	39 (100.0)	94 (93.1)	0.19

Data are expressed as median [IQR] or number (%). TDI score: Threshold Discrimination Identification score, ASA: American Society of Anesthesiologists, ApoE: Apolipoprotein E, GA: general anesthesia

Table 2.14. Baseline and operative characteristics of patients according to their preoperative global olfactory function (TDI score percentile for age and gender).

At three months after the surgery, 38 patients (27.1%) were identified as experiencing a PND: 27 (19.3%) complained from at least one SCC, 7 (5.0%) had a significantly decreased T-MoCA test compared to their preoperative performance, while 4 (2.9%) patients suffered from both SCC and objective cognitive decline. **Table 2.15.** describes the results of the MoCA tests and of the SCC according to preoperative olfactory TDI score. Postoperative T-MoCA was lower in the patients with a preoperative TDI score ≤p25 (*P* = 0.041). 33.3% of the patients (13/39) with a preoperative TDI score ≤p25 complained about one or more SCC in contrast to only 17.8% (18/101) when the TDI score was >p25 (χ^2 (1) = 3.93, *P* = 0.048). We observed an objective cognitive decline in 12.8% (5/39) of the patients with a TDI score ≤p25 and in 5.9% (6/101) of the patients with a TDI score >p25, but this difference was not statistically significant. **Figure 2.12.** details the postoperative neurocognitive situation of the patients according to their preoperative olfactory TDI score.

Neurocognitive testing	**TDI score ≤p25 n = 39**	**TDI score >p25 n = 101**	***P*-value**
Preoperative MoCA-30	25 [24-27]	26 [25-28]	0.28
Preoperative MoCA-22	19 [18-20]	19 [18-20]	0.96
Postoperative T-MoCA	19 [18-21]	20 [18-21]	0.041
Postoperative subjective cognitive concern(s)			
0	26 (66.7%)	83 (82.2%)	0.048
1	9 (23.1%)	8 (7.9%)	
2	2 (5.1%)	6 (5.9%)	
3-7	2 (5.1%)	4 (4%)	

Data are expressed as median [IQR] or number (%). TDI score: Threshold Discrimination Identification score, MoCA: Montreal Cognitive Assessment

Table 2.15. Results of perioperative neurocognitive testing according to preoperative global olfactory function (TDI score percentile for age and gender).

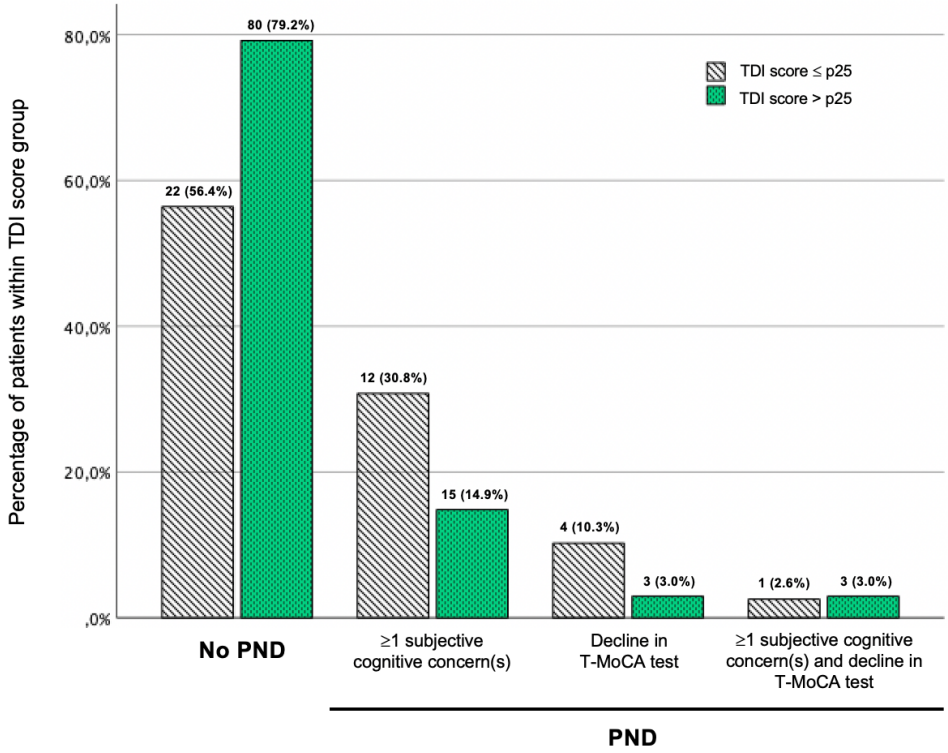


Figure 2.12. Postoperative neurocognitive situation at three months after surgery according to preoperative global olfactory function (TDI score percentile for age and gender). PND: postoperative neurocognitive disorder, MoCA: Montreal Cognitive Assessment, TDI: Threshold, Discrimination and Identification.

In the group with a TDI score ≤p25, we identified 43.6% of the patients (17/39) with PND, whereas they represented only 20.8% (21/101) of the patients in the group with a TDI score >p25 (χ^2 (1) = 7.40, *P* = 0.007). We also analyzed the results according to the three different modalities of the olfactory TDI score (see **Figure 2.13.**). 50.0% (13/26) of the patients with a preoperative identification score ≤p25 experienced PND in contrast to 21.9% (25/114) of the patients with an identification score >p25 (χ^2 (1) = 8.44, *P* = 0.004). We found similar results

regarding the threshold and the discrimination modalities, but the latter did not reach statistical significance.

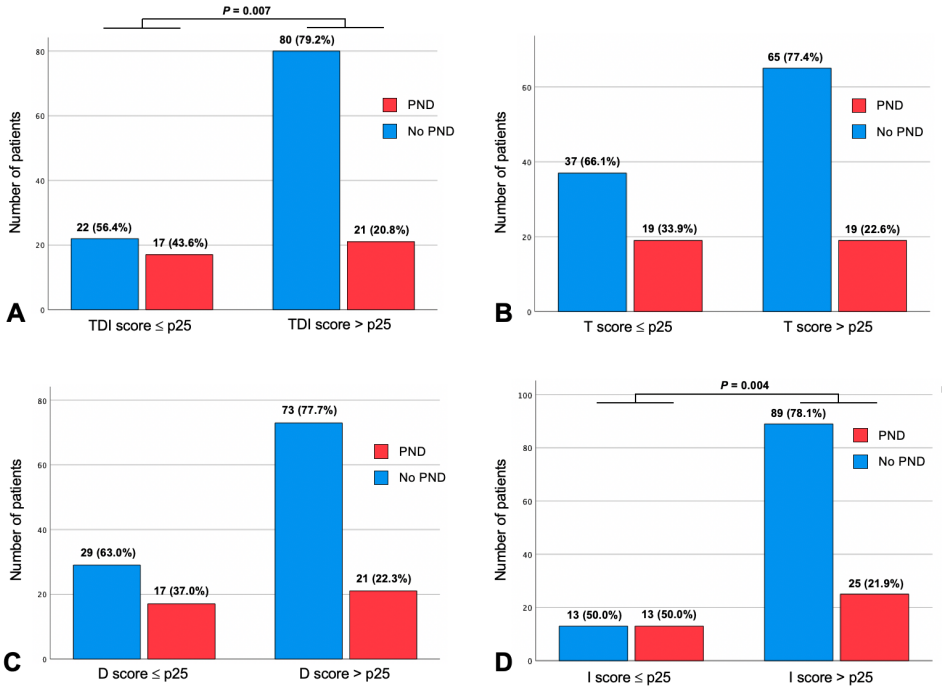


Figure 2.13. Presence or absence of postoperative neurocognitive disorder at three months after surgery according to preoperative olfactory function. (**A**) TDI (Threshold, Discrimination and Identification) score percentile. (**B**) Threshold (T) score percentile. (**C**) Discrimination (D) score percentile. (**D**) Identification (I) score percentile.

We performed univariable and multivariable logistic regression analyses to analyze the association between the preoperative olfactory scores and the presence of PND three months after surgery (**Table 2.16.** and **Table 2.17.**). In the univariable analyses, we found that the TDI score was predictive of PND (OR 0.88, 95% CI 0.82-0.94, $P < 0.001$. This was also the case when analyzing the three olfactory modalities separately, i.e., the threshold, discrimination, and identification scores. Age (OR 1.08, 95% CI 1.02-1.16, $P = 0.016$) and the HADS-

depression score (OR 1.23, 95% CI 1.08-1.41, *P* = 0.002) were also statistically associated with PND.

Variable	OR	95% CI	*P*-value
Preoperative olfactory TDI score	0.88	0.82-0.94	< 0.001
Preoperative olfactory threshold score	0.76	0.63-0.92	0.005
Preoperative olfactory discrimination score	0.76	0.63-0.91	0.002
Preoperative olfactory identification score	0.80	0.69-0.93	0.004
Age	1.08	1.02-1.16	0.016
Female sex	1.59	0.73-3.41	0.24
Lower level of education (≤ 9 years)	2.25	0.90-5.61	0.084
HADS-depression score	1.23	1.08-1.41	0.002
ASA physical status III-IV	1.40	0.66-2.96	0.39
Preoperative MoCA-30	0.87	0.71-1.05	0.14
ApoE ε4 carrier	1.90	0.81-4.45	0.14
Aortic or lower limb revascularization surgery	1.67	0.69-4.03	0.26
Duration of anesthesia	1.00	1.00-1.01	0.38
Use of pre- or intraoperative benzodiazepine	1.16	0.49-2.73	0.73
Sufentanil total dose	2.50	0.07-96.04	0.62
Propofol total dose	0.90	0.70-1.15	0.39
Ketamine total dose	0.99	0.27-3.64	0.99
Sevoflurane-based GA	0.43	0.05-3.72	0.45

OR: Odds ratio, CI: confidence interval, TDI score: Threshold Discrimination Identification score, HADS: Hospital Anxiety and Depression Scale, ASA: American Society of Anesthesiologists, ApoE: Apolipoprotein E, GA: general anesthesia

Table 2.16. Univariable logistic regression analysis for the prediction of the presence of postoperative neurocognitive disorder three months after the surgery

In each multivariable model, we included the olfactory score, the HADS-depression score, a lower level of education (*P* = 0.084 in the univariable analysis), as well as age and female sex, which were both automatically added as confounding variables regarding the olfactory scores. The other variables were not associated with PND in the univariable analyses (*P*-value > 0.1), thus

not included in the multivariable analysis. The higher the preoperative olfactory score was, the lesser the odds of presenting PND, regardless of age, sex, HADS-depression score, and level of education. The HADS-depression score was statistically associated with PND in every model.

Variable	OR	95% CI	*P*-value
Preoperative olfactory TDI score	0.88	0.82-0.95	0.001
Age	1.06	0.99-1.14	0.099
Female sex	2.12	0.88-5.10	0.093
Lower level of education (≤ 9 years)	1.67	0.61-4.55	0.32
HADS-depression score	1.20	1.04-1.38	0.012
Preoperative olfactory threshold score	0.78	0.64-0.95	0.016
Age	1.07	0.99-1.14	0.072
Female sex	1.67	0.73-3.84	0.23
Lower level of education (≤ 9 years)	0.58	0.21-1.61	0.30
HADS-depression score	1.20	1.04-1.38	0.011
Preoperative olfactory discrimination score	0.75	0.61-0.92	0.006
Age	1.06	0.99-1.14	0.99
Female sex	2.08	0.88-4.95	0.097
Lower level of education (≤ 9 years)	0.93	0.33-2.68	0.90
HADS-depression score	1.23	1.07-1.42	0.004
Preoperative olfactory identification score	0.80	0.68-0.94	0.007
Age	1.07	1.00-1.15	0.061
Female sex	2.10	0.88-5.04	0.096
Lower level of education (≤ 9 years)	0.66	0.23-1.84	0.42
HADS-depression score	1.19	1.03-1.37	0.015

OR: Odds ratio, CI: confidence interval, TDI score: Threshold Discrimination Identification score, HADS: Hospital Anxiety and Depression Scale

Table 2.17. Multivariable logistic regression analyses for the prediction of the presence of postoperative neurocognitive disorder three months after the surgery

Sensitivity power analysis

Given our sample size of 139 patients, we obtained a minimal detectable effect size W of 0.24. In our results, we observed an effect size of 0.23. These two values tend to represent a moderate effect size for this analysis [218].

Discussion

This prospective observational trial shows a significant and independent association between preoperative global olfactory dysfunction and the development of PND in older surgical patients. We detected twice as many PND, mainly manifesting as subjective cognitive concerns, in the patients with a poorer TDI score than in others.

Among the 140 patients in our cohort, 27.1% experienced PND three months after elective surgery. This incidence matches that of the literature, which may depend on the type of surgery, study population, follow-up periods, and type of cognitive testing [160][158]. The latter certainly has a major impact in the context of PND investigation. We defined PND as either a subjective and/or an objectively measured cognitive decline. Interestingly, most of our patients with PND complained of SCC (81.6%), whereas we detected only 11 individuals declining significantly their postoperative MoCA test. Recently, there has been growing awareness of the importance of considering SCC, both pre- and postoperatively [219][220][150]. Indeed, having a subjective impression of cognitive troubles is often the prelude to objective decline [221], and may also be the only tangible manifestation of subtle cognitive impairment (i.e., when decreasing the MoCA score by less than one standard deviation in the context of our study). While some SCC are considered to reflect lower memory capacity, others seem to be rather related to depressive symptoms [222], which, in turn, are commonly found in older patients with olfactory dysfunction [81]. Here, we found a higher depression score and more patients complaining about SCC in the low TDI score group. However, adjusting for the depression score in our regression analyses did not attenuate the link between the TDI score and the development of PND. Still, depression was the only other variable associated with PND in our final model, and the exact mechanism driving their "chicken-and-egg" relationship remains a matter of debate [219].

Our results revealed a strong relationship between preoperative olfactory dysfunction and the occurrence of PND. In 2004, Rentowl et al. used a 12-item odor identification test preoperatively but failed to find an association with PND [223]. A minimal sample size might have explained this since only 34 patients completed the study. Moreover, they defined olfactory dysfunction as scoring less than 10, which may have decreased specificity by gathering altogether a wide range of anosmic but also hyposmic patients. The only other study investigating preoperative olfaction included 122 patients tested for postoperative delirium and PND 4-6 weeks after cardiac surgery [210]. In the age-adjusted model, olfactory identification dysfunction predicted PND, but only in patients with poor baseline cognitive performance. According to the authors, the normosmic patients demonstrated a learning effect between testing sessions, which was not the case for the olfactory-impaired individuals. Nevertheless, they showed a significant association with postoperative delirium regardless of baseline cognitive performance. In contrast, we obtained an association between low TDI scores and PND in a sample of cognitively healthy older individuals. The relationship between olfactory dysfunction and postoperative delirium was also confirmed in a small study with Parkinson's disease surgical patients [224] and in a recent trial involving 189 patients undergoing cardiac surgery [225].

The present study and these previously published data highlight olfactory dysfunction as a unique preoperative risk factor for poor postoperative cognitive outcome. The higher the TDI score, the lower the odds of experiencing PND as an older surgical patient, regardless of age, sex, level of education, and depression. Olfactory dysfunction might somewhat reflect some specific brain vulnerability that may not be clinically perceptible at first. Of note, the preoperative MoCA-30 score was not associated with PND in the univariable regression analysis.

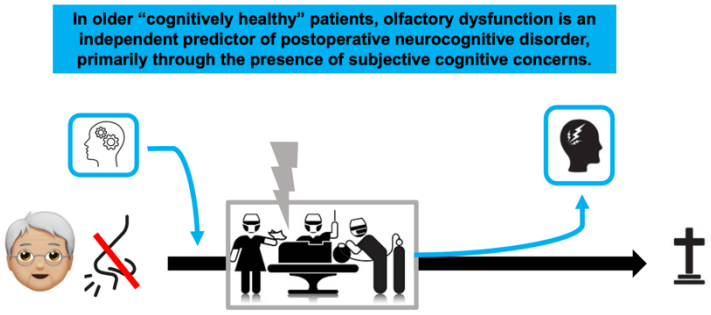
This trial is the first to correlate discrimination and threshold olfactory functions to postoperative cognitive function. Indeed, the aforementioned published studies used solely the identification test, which is more accessible [25]. Each of the three modalities of preoperative olfactory function was associated with PND, with the same pattern of results as their composite TDI score. The discrimination task calls significantly on memory and, just as the identification modality, is related to cognitive executive function, making its association with PND not much of a surprise [189]. The threshold test is less related to cognitive performance but may still require a certain level of attention [211]. Moreover, a lower threshold performance has been recently associated with a reduced MMSE score in a cohort of Chinese community-dwelling older individuals [226]. Whether the threshold task is more cognitively demanding than usually thought or whether this could reveal another mechanism through which olfactory function is related to PND remains unclear.

Anesthetic drugs, notably benzodiazepine and ketamine, were not related to PND in our cohort. First, the use of benzodiazepine was not frequent, and if so, the doses were small. Similarly, ketamine was only used at analgesic doses. Besides, the roles of perioperative benzodiazepine or ketamine in developing postoperative cognitive dysfunction are still widely debated [197][227][228][229]. Carrying the ApoE ε4 allele was not found to increase the risk of PND despite previous evidence [230].

There are several limitations to the present study. First, we did not calculate sample size for the aim of this trial since this was the secondary outcome of a large study. The two effect size values we derived from our sensitivity power analysis were quite similar and confirmed that we could reliably find a moderate effect from our given sample size. Second, the cognitive testing we analyzed included only a single test, the MoCA, and its postoperative evaluation, though being validated as such [200], was realized remotely by telephone. Third, although we reported no difference in PND according to intraoperative drugs,

anesthesia was not protocolized, meaning drugs choice and doses were not standardized. Fourth, and this is a major limitation, we did not systematically use depth of anesthesia monitoring, nor did we collect intraoperative burst suppression data, which could have influenced the occurrence of PND.

In summary, we add new evidence to the predictive role of preoperative olfaction on postoperative cognitive outcome. In older patients, olfactory dysfunction was an independent predictor of PND, primarily through the presence of SCC. Whether preoperative olfactory testing would be a way to assess cognitive reserve and, thus, in some cases, to unveil brain frailty in apparently cognitively healthy individuals deserves attention.



Graphical summary of the main findings from Chapter 4.

SECTION 3 –

OLFACTION AND LEUKOCYTE TELOMERE LENGTH

Chapter 5. Association of olfactory impairment and short leukocyte telomere length: the smell of biological aging?

Victoria Van Regemorter[1,2], Kamar Bouchoucha[3], Philippe Rombaux[4], Thomas Hummel[5], Anabelle Decottignies[3,*], Caroline Huart[2,4,*]

[1]Department of Anesthesiology, Cliniques universitaires Saint-Luc, Brussels, Belgium; [2]Institute of Neuroscience, Université catholique de Louvain, Brussels, Belgium; [3]de Duve Institute, Université catholique de Louvain, Brussels, Belgium ; [4]Department of Otorhinolaryngology, Cliniques universitaires Saint-Luc, Brussels, Belgium; [5]Smell and Taste Clinic, Department of Otorhinolaryngology, Dresden, Germany

[*]Anabelle Decottignies and Caroline Huart contributed equally to this work.

Article in preparation, to be submitted in Rhinology … Soon!

Introduction

Olfactory impairment is a frequent complaint among the general population. Different factors have been reported to influence olfactory function. Among them, age seems to be one of the most prominent, as olfactory function severely declines with aging [24][231]. This age-related decline has often been proposed as a physiological decline of olfactory function. However, this terminology is debatable since some aged people still show excellent olfactory function. Hence, it seems that increased chronological age does not inevitably lead to olfactory decline and that additional factors are involved.

In the last decades, many studies have reported on the intriguing fact that olfactory dysfunction in older individuals is an independent predictor of mortality risk [59][62][64][65][213][232]. Anosmic people are at higher risk of death than normosmic individuals [61] and a recent meta-analysis concluded that olfactory impairment was associated with a 52% higher risk of all-cause mortality [212]. Despite the apparent robustness of the link, the causes remain largely unanswered. In a previous review [12], we summarized the putative underlying mechanisms, notably a more advanced physiological age leading to accelerated brain aging.

According to the WHO definition [233], aging is the consequence of the accumulation of a wide variety of molecular and cellular damages over time. Several hallmarks contributing to the aging process and phenotype have been described [234]. Among them, telomere shortening has been recognized for several years as a contributor to cellular senescence and aging [235]. Telomeres consist of repeated *TTAGGG* sequences located at the end of chromosomes, playing an essential role in chromosomal integrity. In the absence of telomerase, each cell division shortens telomeres, and aging is therefore associated with a progressive shortening of telomeres in somatic cells. Long telomeres are usually considered a sign of good cellular health and better regenerative potential of the

tissues, while, in contrast, abnormally short telomeres are responsible for premature aging syndromes [236].

Human beings are not all equal when it comes to aging. Some 80-year-old individuals are still active and in good health, while others are bedridden. A clinical indicator of biological aging is the concept of frailty, corresponding to a decreased physiological reserve and, therefore, to a reduced capacity to respond to a physical challenge [126]. Frailty status is considered more relevant than chronological age and medical comorbidities when evaluating the risk in older adults [129]. Therefore, when studying the effect of age on the development of diseases or mortality, speaking in terms of biological age and frailty is more accurate than chronological age.

In a recent study performed in older patients undergoing surgery, we found that olfactory dysfunction was significantly associated with preoperative frailty and increased postoperative complications [184]. Our results further revealed that frailty – reflecting advanced aging – might largely underlie this association between olfactory impairment and poor outcome. To gain further knowledge of the mechanisms underlying this link, we aimed to investigate the relationship between telomere length and olfactory function. We hypothesized that olfactory dysfunction could be related to shorter telomere length, possibly through biological aging. To test this hypothesis, we investigated the relationship between telomere length, measured in leukocytes using a Flow-FISH technique, and olfactory function in older people.

Materials and methods

Study population and design

A prospective observational study was conducted at the Cliniques universitaires Saint-Luc (Brussels, Belgium) between March 2021 and December 2022. The

institutional Ethics Committee of Cliniques universitaires Saint-Luc, Université catholique de Louvain (Brussels, Belgium) approved the study protocol on March 3rd 2020 (2020/22JAN/050). We recruited volunteers aged ≥ 65 from our hospital's preoperative anesthesia clinic who were enrolled after receiving an explanation. They all gave written informed consent and were tested before their programmed surgery. Exclusion criteria were the following: a history of neurologic disease (including any type of diagnosed dementia or cognitive impairment), psychiatric disorder, severe head trauma, sino-nasal illness or surgery, and any diagnosed olfactory loss. We did not consider the history of COVID-19 as an exclusion criterion *per se* and considered it as a covariate in our analyses. However, we did not include subjects who reported a recent COVID-19 infection (< 3 months) or complained of a subjective residual olfactory dysfunction.

Olfactory function testing

Each participant underwent the Sniffin' Sticks extended test (Burghart Messtechnik GmbH, Wedel, Germany). We used the n-butanol threshold subtest and the French version of the identification subtest. Threshold (T), discrimination (D), and identification (I) were scored separately on 16 points. We also calculated the global TDI score by adding the results of the three olfactory modalities subtests for a total of 48 points.

We classified these olfactory scores into seven percentiles (p) categories according to the recently updated age- and sex-adjusted norms of the Sniffin' Sticks tests [24]. The categories were the following: (1) ≤ p5, (2) > p5 and ≤ p10, (3) > p10 and ≤ p25, (4) > p25 and ≤ p50, (5) > p50 and ≤ p75, (6) > p75 and ≤ p90, and (7) > p90. We defined olfactory dysfunction as a TDI, threshold, discrimination, or identification score below or equal to the 10th percentile (≤p10) for age and sex.

Leukocyte telomere length measurement

All participants had a blood sample taken the same day they were tested for their olfactory function. Telomere length (TL) was measured by Flow-FISH (Fluorescence *In Situ* Hybridization), which is currently considered the gold standard technique for TL measurement [237]. TL was measured, in duplicate, in granulocytes and lymphocytes in the Cliniques universitaires Saint-Luc as described previously, using the FITC-labelled (*CCCTAA*)3 PNA probe (Panagene) and calf thymus cells as internal controls [238]. Fluorescence was measured with a Navios EX flow cytometer (Beckman Coulter).

We then compared lymphocyte TL measurements to those of a reference cohort of 491 healthy individuals (0 to 99 years) obtained in the Cliniques universitaires Saint-Luc (ISO15189). Short TL was defined as below the 10th percentile for age (< p10). Long TL was defined as equal to or above the 90th percentile for age (≥ p90). Average TL comprised measures equal to or above the 10^{th} percentile (≥ p10) but below the 90^{th} percentile (< p90). Normal TL was described as all measures equal or above the 10^{th} percentile (≥ p10) (i.e., including individuals with long TL).

Covariables

We registered demographic (age, sex, body mass index (BMI)) and olfactory-related (smoking status) characteristics. Three age categories were defined: 65 to 69, 70 to 79, 80, and more. Moreover, we collected medical data known to influence TL, such as arterial hypertension, hypercholesterolemia, obesity (BMI ≥ 30), ischemic cardiopathy, and diabetes. We calculated a depression score with the Hospital Anxiety and Depression Scale (HADS) [201]. All the cohort took the Edmonton Frail Scale (EFS), a validated screening tool for frailty ranging from 0 to 17 points [133]. An individual was defined as frail when scoring ≥ 6/17. This test evaluates nine domains of frailty: functional performance, cognitive

function, general health, functional independence, social support, used medications, nutrition, mood, and continence [132].

Statistical analyses

This study aimed at evaluating the association between olfactory function and leukocyte TL. We ran data analyses with SPSS version 28.0. The Kolmogorov-Smirnov test was used to assess the normality of the data. Ordinal and continuous variables were not normally distributed and were expressed as medians ± standard deviation. We analyzed olfactory scores (TDI, threshold, discrimination, and identification) according to age categories, sex, and smoking status using a Kruskal-Wallis or Mann-Whitney U-test. We realized comparisons between subjects with short TL and normal TL using a Pearson χ^2 for nominal variables and a Mann-Whitney U-test or a Kruskal-Wallis test for ordinal and continuous variables. We performed Pearson χ^2 or Fisher's Exact tests to analyze the association between short TL and olfactory dysfunction. We used multivariable linear regression analyses to assess the association between short TL and the TDI score while adjusting for potential confounding variables. We tested covariables related to TL that were associated with short TL at a threshold *P*-value < 0.2 in our first analysis (obesity, frailty) and covariables usually associated with the TDI score (age and sex). Using a Kruskal-Wallis test, we compared olfactory score percentiles categories between short, average, and long TL. A *P*-value < 0.05 was considered statistically significant.

Results

TL data were obtained using Flow-FISH on lymphocytes isolated from a cohort of 138 participants with a median age of 73.5 years (69-78), including 73 female subjects (52.9%) and 67 past or active smokers (48.6%). Olfaction tests, using Sniffin' sticks, gave olfactory scores for threshold (T), discrimination (D), and

identification (I) of, respectively, 4.4 ± 2.0, 10.3 ± 2.6, and 11.6 ± 2.8. Median TDI score was 26.3 ± 6.2 and, as expected, significantly decreased with age (*P* = 0.037) (**Table 3.1.**).

Characteristics	TDI score (Median ± SD)	*P*-value
Age, year		
65-69	29.25 ± 6.50	
70-79	28.00 ± 6.00	0.037
≥ 80	24.25 ± 5.00	
Sex		
Female	28.50 ± 5.50	0.068
Male	26.50 ± 6.50	
Smoking status		
Present smoker	28.50 ± 6.00	
Former smoker	26.50 ± 6.00	0.41
Non-smoker	26.50 ± 7.50	

TDI: Threshold, Discrimination and Identification

Table 3.1. Olfactory TDI scores depending on baseline characteristics.

Male subjects tended to have a lower TDI score than females, but the difference was not statistically significant. Smoking status had no significant impact on TDI scores. According to original TDI scores cut-offs, most subjects (94/138, 68.1%) were classified as hyposmic (TDI score ≥ 16.5 and ≤ 30.5) while 10 participants (7.2%) were anosmic (< 16.5) and 34 (24.6%) were normosmic (> 30.5). When comparing to normative data for age and sex, 26 subjects (18.8%) had a TDI score below or at the 10th percentile (≤ p10), 32 (23.2%) had a threshold score ≤ p10, 20 (14.5%) had a discrimination score ≤ p10, and 14 (10.1%) had an identification score ≤ p10.

In our cohort, we found 38 subjects (27.5%) with TL below the 10th percentile (< p10), thus referred to as short TL, and 100 (72.5%) with normal TL (≥ p10). The high percentage of volunteers with short TL in our cohort may be related to the

fact that participants were enrolled among patients in the process of undergoing surgery. Alternatively, divergence from our results may be partially explained by the fact that the reference cohort used to build the Flow-FISH curves did not include many older people. Nevertheless, the group with short TL did not particularly suffer more from cardiovascular diseases or diabetes, known to be related to telomere length, than the rest of the cohort [235].

We compared the characteristics of the participants according to their leukocyte TL (short or normal) (**Table 3.2.**). Obesity and frailty status were more frequent in the group with short TL (42.1% vs. 26.0% and 34.2% vs. 22.0%, respectively), but differences were not statistically significant.

Characteristics	**Short TL (< p10) n = 38**	**Normal TL (≥ p10) n = 100**	***P*-value**
Age, year	73 ± 5	74 ± 6	0.36
Female, n (%)	20 (52.6)	53 (53.0)	0.97
Active or past smoker, n (%)	21 (55.3)	46 (46.0)	0.33
History of COVID-19, n (%)	6 (15.8)	18 (18.0)	0.76
Arterial hypertension, n (%)	28 (73.7)	76 (76.0)	0.78
Hypercholesterolemia, n (%)	20 (52.6)	57 (57.0)	0.64
Obesity (BMI ≥ 30), n (%)	16 (42.1)	26 (26.0)	0.066
Ischemic cardiopathy, n (%)	10 (26.3)	21 (21.0)	0.50
Diabetes, n (%)	7 (18.4)	19 (19.0)	0.94
HADS - depression score	4 ± 3	4 ± 3	0.57
Frailty (EFS ≥ 6/17), n (%)	13 (34.2)	22 (22.0)	0.141

TL: telomere length, BMI: body mass index, HADS: Hospital Anxiety and Depression Scale, EFS: Edmonton Frail Scale

Table 3.2. Characteristics of the cohort population depending on leukocyte telomere length.

Among the subjects with a TDI score ≤ p10, 46.2% (12/26) had short TL compared to 23.2% of the subjects with a TDI score > p10 (*P* = 0.018) (**Figure 3.1A.**). When the identification score was ≤ p10, 8 participants (57.1%) out of 14 had short TL, while only 30 out of 124 (24.2%) subjects with an identification score > p10 had short TL (*P* = 0.022) (**Figure 3.1D.**). While showing a similar pattern, the differences regarding discrimination and threshold scores did not reach statistical significance (**Figures 3.1B. and 3.1C.**).

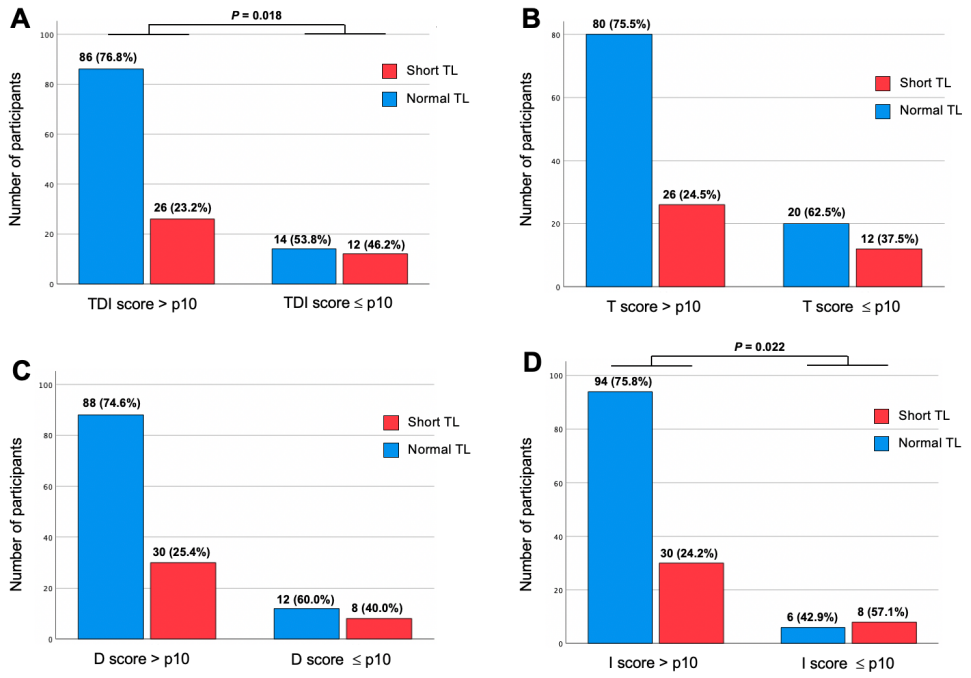


Figure 3.1. Comparison of telomere length according to olfactory scores. (**A**) TDI score. (**B**) Threshold score. **(C**) Discrimination score. (**D**) Identification score. TL: telomere length.

When we compared the olfactory score percentiles categories between the groups according to their TL, short or normal, we found significant differences for the TDI (*P* = 0.036), the threshold (*P* = 0.030), and the discrimination (*P* =

0.010) modalities, but not for the identification score.

We next performed linear regression analyses to associate short TL with the TDI score. In univariable analyses, short TL was significantly associated with the TDI score (*P* = 0.041) (**Table 3.3.**). Adjusting for the BMI had no effect (**Table 3.4.**). The relationship between short TL and the TDI score was attenuated and lost statistical significance when entering the EFS score in the model.

Variable	**Standardized regression coefficient**	***P*-value**
Short TL	- 0.174	0.041
Age	- 0.145	0.090
Sex	- 0.178	0.036
BMI	-0.021	0.80
EFS score	- 0.317	< 0.001

TL: telomere length, BMI: body mass index, EFS: Edmonton Frail Scale

Table 3.3. Univariable linear regression analysis associating short telomere length and covariables with the TDI score.

Variable	Standardized regression coefficient	*P*-value
Short TL	- 0.191	0.022
Age	- 0.183	0.029
Sex	- 0.197	0.019
Short TL	-0.191	0.024
Age	-0.183	0.031
Sex	-0.197	0.020
BMI	-0.001	0.99
Short TL	-0.138	0.089
Age	- 0.108	0.19
Sex	- 0.215	0.008
EFS score	- 0.287	< 0.001

TL: telomere length, BMI: body mass index, EFS: Edmonton Frail Scale

Table 3.4. Multivariable linear regression models associating short TL and covariables with the TDI score.

The group with normal TL included 17 subjects with long TL (≥ p90), representing 12.3% of the whole cohort of the present study. Among this group with long TL, only 1 participant (5.9%) had a TDI score ≤ p10, compared to 25 (20.7%) in the rest of the cohort (*P* = ns). Finally, we compared the olfactory score percentiles categories in the three groups of subjects classified according to their TL: short TL (< p10), average TL (≥ p10 to < p90), and long TL (≥ p90). Statistically significant differences were observed for the TDI, the threshold, and the discrimination scores, which all increased with TL **(Figures 3.2A., 3.2B., and 3.2C.**). While noting a similar pattern for the identification modality, the differences were not significant (**Figure 3.2D.**).

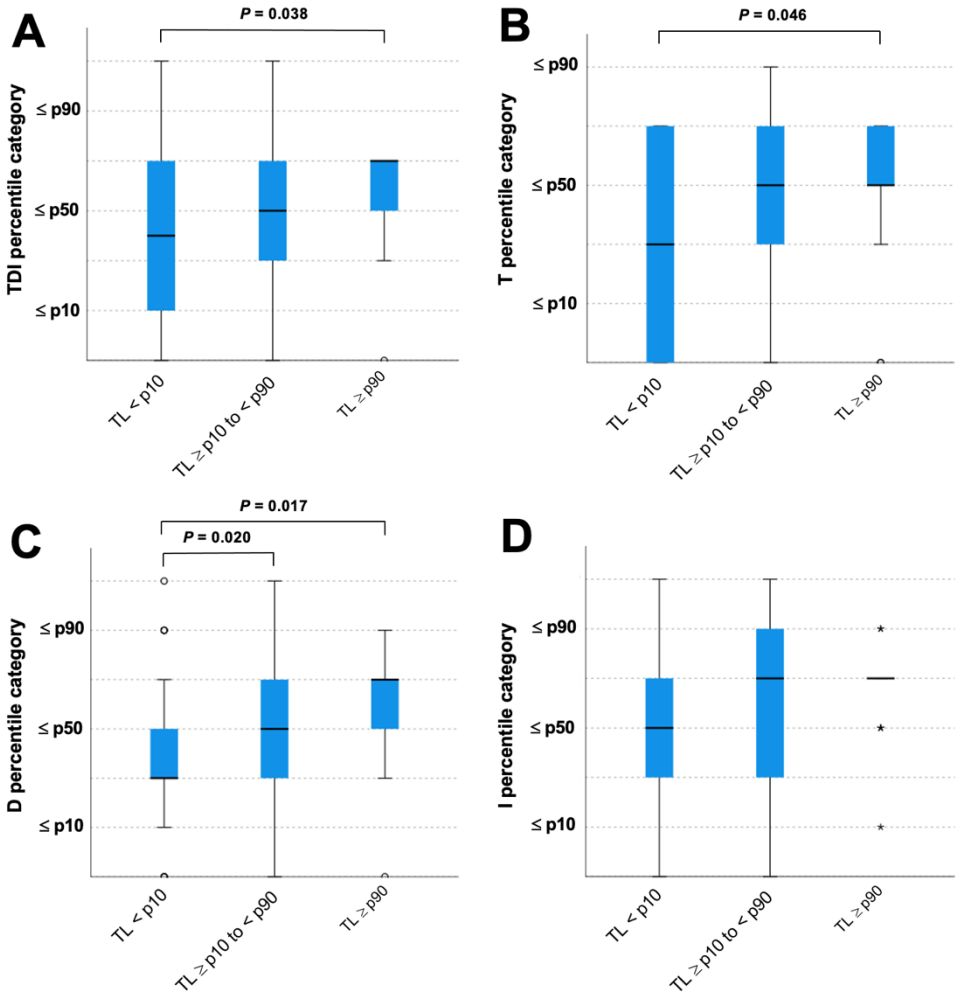


Figure 3.2. Olfactory scores percentile category according to short, average, and long telomere length. **A**: TDI olfactory score. **B**: Threshold (T) olfactory score. **C**: Discrimination (D) olfactory score. **D**: Identification (I) score. TL: telomere length.

Discussion

Our study unveiled a significant association between low olfactory scores and short TL in older individuals. In contrast with the composite TDI score, we did not obtain statistical significance for all separate analyses of the olfactory scores, which may be attributed to a lack of power. Vohra and colleagues recently reported that lower scores at the 12-item Brief Smell Identification Test were associated with short TL – the lowest quartile of their samples, measured with quantitative polymerase chain reaction (qPCR) – in a large cohort of 1603 older individuals [239]. Our study, albeit smaller, strengthens these data with extended olfactory testing and measurement of TL with the gold-standard Flow-FISH technique [238][237]. One of the major drawbacks of the qPCR technique lies in its inability to discriminate between the TL of lymphocytes and granulocytes [240], which is a major issue since aging or diseases affect lymphocytes and granulocytes TL differently [241]. Furthermore, the Flow-FISH technique demonstrates far more accuracy and reliability than qPCR, subject to significant variability [242]. Besides, here, olfactory function and TL assessments were realized simultaneously, as opposed to their asynchronous data collection over a 5-year period [239].

Contrary to previous evidence [243][235], cardiovascular diseases and diabetes were not more common in people with short TL. Although we found a trend towards higher obesity rates, adjusting for BMI did not affect our results. In the study by Vohra et al. [239], data were adjusted for several related illnesses, including diabetes and arterial hypertension. This suggests that these conditions – specifically obesity and diabetes, which have been related to olfactory impairment – may not be responsible for the connection between olfactory dysfunction and short TL.

Interestingly, consideration of frailty hindered the relationship between olfaction and short TL, supporting the idea that they share a common biological component. Although there is clear evidence that frailty is linked to olfactory

dysfunction [203], contradictory results have been reported for TL [244][245]. These studies, however, used qPCR to measure TL and suffered from heterogeneity, especially in frailty assessments. A recent study on Chinese participants aged 75 years and older found no correlation between Fried's frailty criteria and TL [246]. On the contrary, a significant relationship was reported in a younger cohort (40-69 years) [247]. In the present study, frailty tended to be more frequent in older persons with short TL, although this was not statistically significant. Therefore, it seems difficult to associate short TL with frailty [248]. Conclusions may, nonetheless, be difficult to draw based on the fact that, in cohorts of older individuals, there might be a survival bias towards an enrichment of people with reduced frailty. This is in line with a recent meta-analysis, which showed an increased risk of all-cause mortality in people with short TL but with a weaker link in the oldest part of the sample [249]. Altogether, and despite missing a clear-cut answer concerning frailty, these results suggest complex and intricate links between olfaction, TL, frailty, and mortality in older individuals.

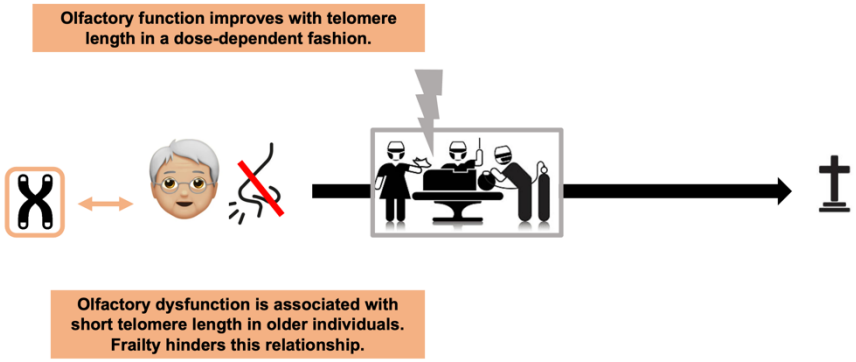
To account for the discrepancies between studies, Sanders and colleagues suggested that TL could be a biomarker of aging in specific tissues rather than at the level of the whole organism [250]. Yet, the olfactory system relies on continuous cellular neurogenesis, and alteration of these processes may account for olfactory decline [34]. A study performed on mice with short TL showed impaired cellular regeneration of the olfactory epithelium when subjected to induced damage compared to wild-type mice with long TL [251]. The olfactory system may thus be more sensitive to short TL than other tissues, which may account for the strong association between olfactory function and TL. Nevertheless, differences in olfactory function were not observed between the two groups of mice in the absence of induced damages, suggesting that, in humans, the link between short TL and impaired olfactory function may only appear with age, when the regenerative potential of the olfactory system may be exhausted by cumulative damages to the olfactory epithelium. It will also be interesting to test whether the protective effects of long TL on olfactory function

are mediated through an impact on the nasal epithelium or on neurons within the brain regions linked to olfaction.

We showed that olfactory scores improved with TL in a dose-dependent fashion. The TDI, the threshold, and the discrimination scores were all higher in people with long TL than the participants with short TL. It is interesting to note that there are still debates about whether longer TL predicts prolonged lifespan [236]. Along this line, long TL could favor certain cancer types [252]. However, research conducted on hyper-long TL mice showed less cancer incidence and increased longevity [253]. In humans, long TL was more frequent in the oldest old, probably reflecting a survivor effect [254]. Furthermore, "healthy" centenarians tend to have longer TL than "unhealthy" ones [255]. Nevertheless, the fact that a better sense of smell and longer TL are related provides mutual evidence for both being indicators of aging.

This study has several limitations. As discussed earlier, some results probably suffered from a small sample size. Besides, our cohort was composed of preoperative patients, which may have influenced our results. In our analyses, we used only one screening tool, the EFS, to evaluate frailty status.

In conclusion, we found a positive correlation between global olfactory function and telomere length in older individuals. Our findings provide further evidence for the intricate – but still not fully elucidated – links existing between sense of smell, telomere length, and frailty. Additional studies are needed to fully understand the significance of these markers as hallmarks of biological aging.



Graphical summary of the main findings from Chapter 5.

SECTION 4 –

DISCUSSION AND PERSPECTIVES

Foreword

Getting to know better the "special sense through which odors are perceived", aka *olfaction*, has been quite an exciting journey ...

Our primary objective was to understand the mechanisms underpinning this intriguing relationship between olfactory dysfunction and increased mortality risk in adults. The 1-year postsurgical outcome in our studies was mainly marked by morbidity, not mortality, thankfully for the kind participating patients. This did not prevent us from obtaining significant results that reinforced some of our baseline hypotheses [12]. So now, what do we genuinely believe drives the link between poor smell and worse outcome? Assessing the olfactory function of perioperative patients provided new evidence on its link with physical frailty, cognition, and cellular senescence. In the end, are they not all actors in the same story? Are they not all somewhat connected inside a greater entity of body and brain vulnerability?

Testing the olfactory function of the patients waiting to undergo elective surgery is uncommon, to say the least. Today, and with great dismay, healthcare providers must deal with a lack of time, performance obligations, and financial issues. Is preoperative olfactory testing feasible in real life? But, above all, is there a point?

Before discussing the perspectives of this work, I wish to make a short digression. A few weeks after I finally got the authorization from the Ethical Committee to start including patients, we were instructed to stay at home because of a highly contagious killer virus spreading all over the world. The icing on the cake, this virus would turn off the sense of smell in most infected people. If we were to return to “normal life”, how could the objectives of this work be properly fulfilled in an anosmic population? Looking back over the past four years, COVID-19 did not have the impact I initially thought it would have on my thesis. For the first part of my work, very few older people had contracted the

virus because they were mostly staying cloistered at home. As to the second study, we enrolled some patients – representing 14% of the cohort – who had once tested positive for COVID-19 but had no lasting subjective olfactory impairment. We included COVID-19 as a covariable in our analyses, but fortunately, it did not influence any of our results. In all of this, beyond slowing down the recruitment phase, COVID-19 has not represented that much of an issue here.

What truly underlies the link between olfactory dysfunction and worse outcome?

We now firmly believe that *frailty* is the main factor driving the relationship between poor smell and bad outcome in older individuals. But what is really hidden behind these seven letters? Conceptualizing frailty is challenging, as so many definitions and diagnostic tests exist. By traveling across the possible mechanisms we had previously formulated [12], we will discuss their implication and, especially, their connection to frailty. Lastly, by exploring the facets of *frailty* differently, we wish to propose a more global vision of the interplay between olfactory impairment, physical frailty, cognitive impairment, cellular senescence, and, ultimately, outcome.

The first hypothesis appearing in our narrative review concerned the direct effects of a decline in smell on the human body [12]. First, the negative consequences on our "eating experience" may certainly have a role [256]. Everyone has already felt the despair of not tasting anything of a meal when suffering from a simple cold. Unfortunately, we could not collect precise data about food intake and nutrition markers in our studies. Besides, some debates may remain regarding olfactory impairment and malnutrition in the geriatric population [32]. Nevertheless, we do know that the chronic undernutrition that may arise from eating less – or not adequately – will lead to weight loss, sarcopenia, and, more generally, physical frailty [129]. Weight loss itself is, in fact, a mediating factor in Liu's study [65].

The preliminary results of our second study showed an effect of depressive symptoms. The fact that a lack of social physical contact – which may also be related to depression – in olfactory-impaired women could contribute to the increase in mortality adds another argument for a direct effect of olfaction [84]. Pang et al. suggested that depression could impair olfaction and increase mortality risk through inflammatory cytokines [212]. Indeed, cytokines levels are higher in patients suffering from major depression, as well as in older adults with

olfactory dysfunction [257][258]. Yet, chronic low-grade inflammation and immune activation may contribute to the development of frailty [259]. However, one study discovered a specific plasma cytokine signature related to olfactory dysfunction that differed from that of physical frailty [258]. In contrast, increased IL-6 levels were found to have a potential role in the association between self-reported olfactory impairment and frailty [107]. Hence, how chronic inflammation may underlie the links between all the components interacting in a larger frailty concept remains unanswered.

Medical illnesses have known associations with olfactory impairment [50][12]. Statistically speaking, they were found to either mediate slightly or have no effect on the olfaction and mortality link, both in previous studies and in our work [61][62][184]. Obviously, one cannot deny the impact of comorbidities on the life expectancy of older adults. What we should not miss here is that, rather than the diseases per se, it is the way the body responds to medical comorbidities – and thus its physiological reserve – that will determine the relevance of medical diseases. In a large study on adults over 65, people who were diagnosed as frail by the physical frailty phenotype had a higher risk of death than frail people classified as such with the frailty index [208]. This supports the idea that an accumulation of health deficits is a poorer reflection of the vulnerability of individuals. Besides, our work confirms the fascinating finding that olfactory impairment predicts worse outcome regardless of age and medical illnesses. This is a supplementary argument for incorporating the sense of smell into a new frailty construct.

It makes no doubt that olfaction is closely connected to cognition and that it drives, at least partially, the relationship between poor smell and worse outcome [65][12]. Indeed, in this work, preoperative cognition lost its predictive ability of postoperative complications in multivariable analyses containing olfactory function. This suggests that olfaction would account for cognitive function. We also found that preoperative olfactory impairment predicts poor postoperative

neurocognitive function, and that cognitively-impaired patients experience a decline in their immediate postoperative olfactory function. A recent trial found that olfactory dysfunction was associated with impaired baseline cognition and a greater incidence of postoperative delirium [225]. Overall, these findings indicate that olfactory function provides reliable insight into the older population's cognitive reserve. Furthermore, preoperative frailty is a proven risk factor for postoperative delirium in older surgical patients [260][261]. Cognitive vulnerability and physical frailty are both strongly linked to olfactory function and should stand together as they share common mechanisms [167][184].

At the cellular level, Xiao and colleagues recently proposed that the olfactory epithelium regenerative dysfunction caused by telomere shortening could constitute one of the underlying mechanisms in the pathway to mortality [256]. We believe that the relationship between smell and telomere length may go far beyond this. Our data provide new evidence to support links between short telomere length, olfactory impairment, and physical frailty. Again, medical comorbidities do not seem to be the driving factor here. A small prospective trial involving patients undergoing spinal deformity surgery detected preoperative shorter telomere length in the patients developing postoperative complications [262]. Telomere shortening may thus reveal itself as an indicator of vulnerability when facing stressful conditions. A large study found that the combination of short telomere length and physical frailty had a substantial synergistic effect on their predictive ability of long-term all-cause mortality [263]. Therefore, this suggests that physical frailty and short telomere length could involve distinct mechanisms of biological aging, each deserving a unique place in a broader *frailty* construct.

In our two trials regarding poor postoperative outcome, physical frailty consistently had the greatest impact on the predictive power of olfactory function [184]. Overall, our work offers compelling arguments for a strong connection between olfaction – potentially to different extents for threshold, discrimination,

and identification – and *frailty*. When comparing the physical frailty phenotype and the frailty index to identify frail individuals, the highest agreement was found in the most vulnerable adults, probably ticking many boxes of frailty aspects [208]. Olfactory function could in fact rally various facets of frailty and, hence, could be reasonably integrated into a larger frailty assessment tool, as also suggested by Nagururu et al [203].

In **Figure 4.1.**, we propose an enlarged *frailty* concept encompassing olfactory impairment, short telomere length, physical frailty, and low cognitive reserve. We also illustrate the complex interplay between these components, which may imply – in different ways and non-exhaustively – comorbidities, depression, undernutrition, or cognitive impairment. Finally, they all somehow constitute surrogate markers for the vulnerability that may affect older individuals in the course of biological aging.

In the perioperative context, improving our assessment of *frailty* will give us a better grasp of a patient's capacity to cope with the stressful event of surgery. In the end, it is all about trying to decrease the burden of surgery on both the brain and the body. Hopefully, optimizing the identification of high-risk patients – who would maybe benefit from prevention strategies – may be a start, even if there is still some way to go in accurately predicting postoperative complications.

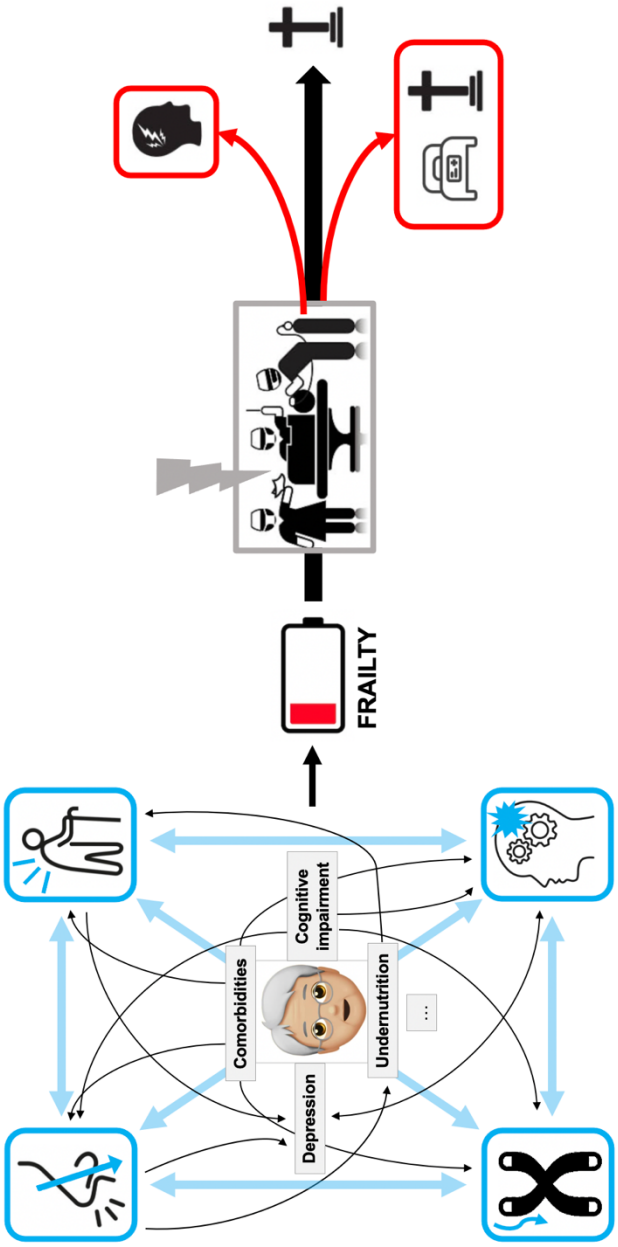


Figure 4.1. Illustration of our proposed novel understanding of *frailty*. In older individuals, olfactory impairment, short telomere length, physical frailty, and low cognitive reserve are all closely linked to one another. These markers of vulnerability may plant the seeds of poor medical and cognitive outcome after surgery.

Preoperative olfactory testing: is there really a point?

Although healthcare providers recognize frailty's value, the use of screening tests is still limited [264]. Yet, as mentioned above, accurately detecting a frail patient is a fundamental first step before considering any intervention strategy targeting frailty itself or its damaging health consequences [208]. The considerable panel of frailty tests available reflects again the complexity of this concept. In addition to our findings and previous discussions, the fact that olfactory function has been associated with many of them supports the idea that smell itself could serve as a "bellwether" of frailty [204].

While we have emphasized at length the necessity of preoperative frailty identification, we must acknowledge its relatively weak potential in predicting poor postoperative outcome [217]. The positive correlation, as strong as it may be, between a test and a specific outcome does not automatically imply performance in discriminating whether a patient will or will not develop the outcome. Then, what about the performance of olfactory function evaluation? The answer to this question is twofold and depends on the type of surgical population – and thus the incidence of postoperative complications – we are considering.

First, let's discuss patients who undergo vascular surgery. In our cohort, half of them eventually developed postoperative complications. As anesthesiologists, we are well aware of the high rate of morbidity and mortality occurring in the perioperative course of these frail patients [214][265]. Therefore, in any case, we already plan to provide these patients with very meticulous anesthesiologic care. The value of olfactory testing in this population comes from its high positive predictive value (77.8%), meaning that most patients with a poor sense of smell will suffer from postoperative morbidity. For instance, if we are unsure whether there is a benefit in planning postoperative monitoring in the intensive care unit or keeping the patient one more night in the hospital, the presence of olfactory dysfunction could help tip the scale. Indeed, intensive care monitoring or even

longer in-hospital stays carry heavy implications regarding healthcare costs and resource use, which prevent their application for every surgical patient.

When we analyze the data of patients who had hip or lower back surgery, complications only affected one out of five patients after one year. In case of a lower postoperative incidence, olfactory impairment, much like frailty screening tests, has actually poor discriminative power regarding the occurrence of morbidity and mortality. In contrast, preoperative olfactory testing shows benefit in the high negative predictive value of normosmia (90.7%). Normosmic patients will rarely suffer from postoperative complications. As a result, they are the ones who could safely participate in Enhanced Recovery After Surgery (ERAS) outpatient programs, which are now being implemented for surgeries such as total hip replacement [266]. This kind of program may enhance patient satisfaction and surgical outcomes while minimizing costs and resource usage [267].

As anesthesiologists, we stand in a unique position to develop "value-based" care in the surgical setting, which fosters both better patient outcomes and cost-effectiveness [268]. In this evolving paradigm of perioperative medicine, olfactory testing may thus have a part to play in categorizing the patients based upon their risk to personalize pathways. Also, with improved patient selection, we can switch from reactive medicine towards setting up preventative programs early in the preoperative period. In fact, this goes further than simply aiming to reduce morbidity directly linked to the surgery event in question. Instead, it is more about improving patients' health to prevent them from needing the next – certainly more invasive – surgical procedure [269].

To illustrate our point, could we imagine including olfactory-impaired patients in a preoperative cognitive training program? Even if such programs are still under investigation, some studies have shown a potential impact on postoperative neurocognitive disorders [270][271]. Yet, we believe that the sense of smell may be an opened window directly into the brain's cognitive reserve. Indeed, in our

study, olfactory testing is more discriminative than the MoCA test in predicting postoperative neurocognitive disorder in – a priori – cognitively healthy individuals. Olfactory testing could be valuable for selecting the patients who could gain the most from cognitive prehabilitation. What about olfactory training? Perspectives on its – certainly mild – cognitive effects are encouraging [100][272] but more evidence is needed before we can rejoice. As to “improving” physical frailty, there is no existing data but it seems rather unlikely that olfactory training could have a real influence.

More specifically, our data highlight the link between preoperative olfactory dysfunction and the apparition of subjective cognitive concerns after surgery. Though not given due recognition in the past, subjective impairment must be considered a poor cognitive postoperative outcome [161]. Besides, this is especially true in a patient-centered, value-based system. This year, Li and colleagues undertook the quite unconventional task of analyzing *The Guardian's* website user comments that were submitted under a journalist – David Cox – article entitled: "The hidden long-term risks of surgery: "It gives people's brains a hard time"", published in April 2022 [273]. When reading the comments, we understand that lay people tend to focus more on subjective symptoms and their emotional impact. The authors extracted this particular comment, which says it perfectly: "*I just want my brain back, it was a great brain, and I miss it*". Yet, unfortunately, the people reported encountering a dismissive attitude from healthcare providers regarding these complaints. What was also pointed out is the missed preoperative opportunity to warn people about these potential cognitive changes after surgery [273]. As perioperative physicians, we must increase our awareness of the negative cognitive experiences our patients may undergo. Preoperative olfactory function testing may allow us to hold meaningful information as to postoperative cognitive risk, which, in turn, may be explained and discussed with the patients before they get their surgery.

Speaking of patient experience, olfactory function testing has been globally well received by preoperative patients. Besides, the COVID-19 pandemic has raised awareness about the importance of smell, increasing people's curiosity about their own olfactory function. Most people found joy and distraction in smelling the odors (apart from the fish odor, let's be honest). Yet, we should not underestimate the impact of preoperative anxiety in older patients. In the eternal pro-con debate for benzodiazepine administration, every small distractive technique may have value before surgery [274].

However, testing all three olfactory modalities may be burdensome in an older population. The threshold test may be particularly taxing [211]. Moreover, also from our experience, the discrimination task is often lengthy. Considering our work's engaging results, we should concentrate our future efforts on the pragmatic implementation of olfactory testing. While analyzing data for the three subsets of olfaction increased our findings' robustness, it also demonstrated the reliability of the identification test in representing global olfactory function in the domain of perioperative *frailty*. From a clinical point of view, the identification subtest offers numerous advantages. Besides being amusing and easy to follow for the patient, it is quick, bedside-friendly, and simple to administer [25]. Therefore, at a time when healthcare resources and time must be judiciously used, focusing on the olfactory identification function seems a reasonable option in the perioperative clinical setting.

Then, how are we planning to define the "best" preoperative olfactory identification test? One goal could be to transpose our findings obtained from the global TDI score into adjusted reliable cut-offs for use with the identification test alone. For instance, we show that orthopedic patients with a global TDI score of 30.5 or higher have a significantly lower likelihood of experiencing postoperative complications. For which value of the 16-point identification score may we get the same significant information?

Furthermore, we may wonder whether some odors could have better discriminative power than others. We had actually found quite noteworthy results in our first study using exclusively the Sniffin' Sticks 12-item identification [184]. We could then imagine picking out the most effective odors of the 16-item test to create a smaller, yet equally reliable, identification screening test. In the study by Cao and colleagues, they found the ability to smell "coffee" to be significantly associated with 10-year mortality [232]. The participants who could not recognize coffee – which was, in fact, the most correctly identified odor in this Chinese cohort – may then be more likely to actually suffer from olfactory dysfunction [256]. Along these lines, a brief coffee smell identification test has also recently been shown to increase the sensitivity of the MMSE in accurately detecting cognitive impairment [275]. On the other hand, the familiarity of turpentine smell seemed low in our cohort and has been shown to drop in much younger populations [276], which may question its significance in a screening test. These few findings may open avenues for subsequent odor-specific research. Indeed, further investigations – both in our database and in future studies – must be undertaken before making any premature assumptions about the potential superiority of one smell over another. Besides, we should take into consideration that perceptions of smell can vary across different cultures [277].

What about the test-retest reliability of such a test? This is especially relevant for clinical use and when considering the dynamic process of aging. Both the 16-item and the 12-item versions of the Sniffin' Sticks identification test have shown good performance in that matter [25][278]. Still, the more odorants we test, the higher the test-retest reliability. Therefore, we should also keep this in mind while determining the "best" preoperative olfactory tool.

One last point should retain our attention. Typically, administering a test – of any kind – requires the need for a trained healthcare professional to spend time with the patient. As mentioned earlier, the olfactory identification test is neither complicated nor long to administer. Still, with a view to optimizing resources and

time, we might want to take the potential of olfactory screening a step further. Self-assessment with the Sniffin' Sticks seems a feasible option for the identification subset, even in older or olfactory-impaired participants [279][280]. Thus, we could imagine setting up a dedicated space for preoperative patients to self-assess their olfactory identification function just before having their anesthesia consultation. Otherwise, "scratch and sniff" olfactory screening tests have been developed, among which the Pocket Smell Test containing 8 odorants or the Brief Smell Identification Test using 12 items derived from the University of Pennsylvania Smell Identification Test (UPSIT) [281][282]. Self-assessment is made a lot easier with this kind of test since they are specifically designed to that end. In this case, we could simply send the patient one test to complete before coming to the anesthesia preoperative visit. Nonetheless, the high cost of these tests (from 10 to 20 €, excl. VAT, per each test) is likely to limit their use in the current healthcare paradigm.

Epilog

Let's face it: the perfect test does not exist. We cannot detect every frail patient, and we do not possess the crystal ball that could foretell what will happen after surgery. At least not completely. At least not today.

Yet, this thesis presents a unique and innovative approach to assessing preoperative older patients. At our small level, we managed to demonstrate the value of olfactory testing in older patients scheduled for surgery. Aside from composing the perfect blend of odors to assess, defining the rightful place of olfactory function in the perioperative care algorithm will definitely constitute the next real challenge.

From a more theoretical point of view, we put a name on what we believe mainly drives the road between poor smell and increased death. Across the perioperative spectrum, and with a little dive into cellular biology, we share a more comprehensive understanding of the famous culprit, that is *frailty*. Olfactory dysfunction, physical frailty, low cognitive reserve, and, finally, short telomere length are all interconnected pieces in the giant puzzle of true aging. Undoubtedly, there are still some missing pieces here, but hopefully, those will be identified soon enough. Meanwhile, we shall adopt this wider *frailty* construct when taking care of the older patient in front of us.

Our journey does not end here. This work reinforces once again the singularity and multifaceted nature of the sense of smell. We intend to keep discovering the many unexplored features olfaction has in store for us. Who would have ever bet that anesthesiologists would need to test their patients' olfactory function before surgery?

The future smells good … Be prepared to sniff, people!

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