GEOGRAPHY OF MEDICATION REIMBURSEMENTS IN BELGIUM: AN EXPLORATORY ANALYSIS

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Geography of medication reimbursements in Belgium: an exploratory analysis

Géographie des remboursements de médicaments en Belgique : une analyse exploratoire

Geografía de los reembolsos de medicamentos en Bélgica: un análisis exploratorio

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Résumés

English Français Español
As part of a broader multidisciplinary research project dealing with the association between health and green/blue environments, this paper aims at exploring the spatial variation of medication reimbursements within Belgium. These data were potentially and a priori considered as a proxy for health. This paper is purely exploratory: statistical maps, correlations, PCAs and cluster analyses corroborate the results.
Five groups of medications prescribed for health disorders associated with the environment have been selected. We show that – at the level of the municipalities – the spatial distributions of the five medication groups are positively correlated to each other (medication consumption co-vary positively in space, whatever their type), but are independent of the environmental and socio-economic conditions measured. Against our expectation, they prove to be negatively correlated to air pollution and green spaces.
Strikingly, the spatial distribution of medication prescriptions follows the linguistic border between Flanders and Wallonia. This implies that the observed differences are mainly due to administrative/political regional differences in terms of health policies, medical schools, pharmaceutical commercial activities, etc. that are hard to quantify (no data, diversity of actors) but should be taken into account in any further explanatory model. Medication reimbursements data correspond to a new type of data, and despite their potential attractiveness for health analyses, extreme care has to be taken when interpreting their spatial variation and their link to health.

Cet article s'inscrit dans un projet de recherche multidisciplinaire visant à étudier la relation entre santé et environnement (espaces verts/bleus), et explore tout particulièrement la variation spatiale des remboursements de médicaments prescrits en Belgique. Ces données ont initialement été considérées dans ce projet comme des estimateurs potentiels de la santé.

L'analyse se veut essentiellement exploratoire : des cartes statistiques, des coefficients de corrélation, des ACP et des analyses de classification corroborent les résultats.
Cinq groupes de médicaments prescrits pour des problèmes de santé associés à l'environnement ont été retenus. Nous montrons que les distributions spatiales des cinq groups de médicaments sont positivement corrélées entre elles (quelle que soit la maladie, les consommations de médicaments co-varient positivement dans l'espace), mais elles sont indépendantes des conditions environnementales et socio-économiques mesurées à l'échelle des communes. Elles sont même négativement corrélées à la pollution de l'air et aux espaces verts.
De façon inattendue, la distribution spatiale suit la frontière linguistique entre la Flandre et la Wallonie. Ceci signifie que les différences observées dépendent de conditions administratives/politiques régionales et donc de politiques de santé, d'écoles de médecine, d'activités commerciales des firmes pharmaceutiques, etc., autant d'éléments extrêmement difficiles à quantifier (pas de données, diversité des acteurs) mais qui devraient être pris en compte dans tout modèle explicatif. Nous en déduisons que si les données de remboursement des prescriptions de médicaments constituent une nouvelle source potentiellement utile, une grande prudence reste de mise quant à l'interprétation de leur variation spatiale et leur lien avec la santé.

Este artículo se enmarca en un proyecto de investigación multidisciplinaria enfocada a estudiar la relación entre la salud y el medio ambiente (espacios verdes / azul) y, en particular, explora la variación espacial de los reembolsos en medicamentos recetados en Bélgica. Tales datos se consideraron en un principio como posibles estimadores de la salud y cuyo procesamiento, resultados y análisis se desarrollan a partir de un enfoque esencialmente exploratorio: mapas estadísticos, coeficientes de correlación, ACP y análisis de clasificación. Se seleccionaron cinco grupos de medicamentos recetados por patologías de la salud vinculadas al medio ambiente. Se expresa que a escala comunal las distribuciones espaciales de esto grupos están correlacionadas positivamente entre sí (independiente de la enfermedad, el consumo de estos covaría positivamente en el espacio), pero son independientes de las condiciones ambientales y socioeconómicas, incluso se correlacionan negativamente con la contaminación del aire y áreas verdes. Inesperadamente, la distribución espacial sigue la frontera lingüística entre las regiones Flamenca y Valonia, significando que las diferencias observadas dependen de las condiciones administrativas / políticas regionales y, por tanto, de las políticas de salud, facultades de medicina, estrategias comerciales de las empresas farmacéuticas, etc., Todos elementos extremadamente difíciles de cuantificar (sin datos, diversidad de actores) pero que deberían ser considerados en cualquier modelo explicativo. Deducimos que, si bien los reembolsos de prescripciones de medicamentos son una nueva fuente de datos potencialmente útil, se debe tener elevada precaución al interpretar su variación espacial y vínculo con la salud.

Entrées d'index

Mots-clés : santé, géographie de la santé, cartographie, comportement spatial, frontière
Keywords : health, health geography, cartography, spatial behavior, border
Palabras claves : salud, geografía de la salud, cartografía, comportamiento espacial, frontera

Texte intégral

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1. Introduction

1 Living environment and health are closely associated. Among others, salutogenic effects of the proximity to green spaces have been largely demonstrated on physical and mental health (see e.g. Ulrich, 1984 ; Sacker and Cable, 2005 ; Nielsen and Hansen, 2007 ; Maas *et al.*, 2009 ; Van Herzele and de Vries, 2012 ; Gascon *et al.*, 2015 ; Pietilä *et al.*, 2015 ; Mukherjee *et al.*, 2017), while high levels of air pollutants such as PM_{10} or NO_2 are associated with respiratory and cardiovascular problems and consequent medication intakes (see e.g. Casas et al., 2016 ; Sofianopoulou et al., 2013). Recent studies insist on additional adverse effects of air pollution on the brain, birth outcomes

(e.g. low birth weight) or metabolic disorders like diabetes mellitus (Landrigan *et al.*, 2017 ; Thurston *et al.*, 2017).

2 The association between environment and health is most often investigated at the local level and within selected urban areas (see e.g. Cheng et al., 2011), in particular when tackling issues of increasing urban population, for targeted policies and investments on green infrastructures (Conway *et al.*, 2010 ; Coutts and Hahn, 2015 ; Adli *et al.*, 2017). City dwellers are generally considered as living in less healthy environments, while enjoying the proximity of a large variety of facilities. Non-urban areas, experiencing lower built-up densities are generally considered as healthier environments, although they also suffer from some types of pollution due, for instance, to industrial or agricultural practices (Paulot and Jacob, 2014), including intensive animal breeding or the use of pesticides. Studies analyzing spatial variations at the level of an entire country are, however, very scarce (Henau *et al.*, 2015).

3 Health status is generally proxied by different types of data such as individual perceived health obtained from surveys (Maas *et al.*, 2006 ; Triguero-Mas *et al.*, 2015), hospital records (Dadvand *et al.*, 2012 ; Pereira *et al.*, 2012), and more recently by medication prescriptions (Halasa *et al.*, 2002 ; Naughton, Bennett and Feely, 2006 ; Bianchi *et al.*, 2009), or data derived from time-series and cohort studies, in the case of mortality (Samet and Krewski, 2007). Although medication prescriptions have been used in the literature for specific medications, mapping their spatial variations is quite novel and rare (Cheng *et al.*, 2011). Here, werefer to Wangia and Shireman (2013) for a meta-analysis on the application of GIS tools for analyzing spatial variations of medication prescriptions. The vast majority of studies have investigated spatial variations of health by looking at individual morbidity or mortality causes, rather than looking at their covariation in space (see e.g. Waldhoer et al., 2008).

4 In a sister paper, we described the spatial variation of asthma medication prescriptions for preschoolers (0-5 years old) in Belgium (Trabelsi *et al.,* 2019); the paper uncovered clear spatial structures for the prevalence of asthma, but it also revealed that the spatial structure of the medication cost per case differed substantially from that of the prevalence. The present paper deals with a larger number and variety of health disorders (via ATC medication codes) and considers all age groups. We a priori presumed that the history of the Belgian economic and social development (former coal mines, etc.), the urbanization level, the social realities, have generated concentrations of specific diseases, and hence over/under consumptions of specific types of medications. Here, we conduct exploratory spatial data analyses (E.S.D.A.) to describe the spatial distribution and clustering of age standardized prevalence of medication purchases in Belgium for five groups of medications and their correlation with environmental and socio-economic variables.

2. Data and method

2.1 Medication purchases

5 Health insurance is compulsory in Belgium and most residents (98%) are enrolled in the Health Security System. In other words, a very small part (2%) of the population living in Belgium is not covered by the social security system and therefore, not included in this study. These correspond to undocumented immigrants, people with complex social problems (such as homelessness), or employees of international bodies (EU, NATO, etc.). Most health care expenditure including medication prescribed by physicians is reimbursed (at least in part) by one of the seven Belgian health insurance funds. The Intermutualistic Agency (IMA-AIM) is an umbrella organization that centralizes all information on health care reimbursements collected by all Belgian health insurance funds. Information on reimbursed medication is coded using the ATC (Anatomical Therapeutic Chemical) code (see WHO Collaborating Centre for Drug Statistics Methodology, 2018). After medication prescription by a medical doctor and

the purchase of that medication in a pharmacy located in Belgium (including hospital pharmacies), the ATC codes are registered in the health insurance system. The database does not include non-reimbursable medications and medications that do not require a prescription.

6 In this analysis, medication reimbursement information is provided at the municipality level for all 589 municipalities of Belgium and concerns all individuals having purchased one of the studied prescribed drugs at least once in a calendar year (here named "*a case*"). Information on its actual use, frequency of use, or about co-morbidities, meaning here the presence of the same individual in more than one medication group, cannot be deducted from the data. In addition, this database does not provide information on the frequency of purchase of the medication for one year. We know that the intensity of use of a medication could lead to other spatial structures (see Trabelsi *et al.* 2019).

7 Prevalence is here defined as the number of *cases* divided by the total population registered in each municipality. Age-standardized prevalence is expressed per 100 inhabitants (Age-Standardized Medication reimbursement Prevalence, noted here ASMP). It is provided separately for men and women (see Costa, Bauwelinck and Deboosere, (2019) for details about computation) as it is presumed that health disorders are often gender specific (Glaeske *et al.*, 2012 ; Che *et al.*, 2014 ; Skoog *et al.*, 2014). In order to minimize the effects of small numbers generating statistical and privacy issues, an average prevalence is computed over 3 years (2012-2013-2014).

8 We here limit our investigations to five medication groups corresponding to common health disorders, managed at the level of primary care, and that are a priori related to environmental conditions, according to the epidemiological literature (see e.g. Thurston *et al.*, 2017 ; Fong, Hart and James, 2018). **Table 1** presents the target system, the ATC codes, the name of the codes and the abbreviations used in this paper for each medication group. *RS* includes medications for respiratory obstructive diseases such as asthma or Chronic Obstructive Pulmonary Disease (COPD). *CVS* includes medications used to reduce blood pressure or treat other cardiovascular problems such as ischemic diseases. *LIP* includes medications prescribed to reduce hyperlipidemia, while *IS* includes medication for treating allergy symptoms (local and systemic). Finally, *CNS* includes drugs acting on the central nervous system mainly indicated to treat symptoms of anxiety and depression. Nevertheless, it is important to highlight that some of the listed medications may be used for different disorders [e.g. diuretics (C03) can be used to reduce blood pressure as well as for some renal disorders] and hence their specificity is not absolute.

Table 1 : Five groups of medications used in this study.

	Target system	**ATC code**	**Name**
RS	**Respiratory system**	R03	Drugs for obstructive airway diseases
CVS	**Cardiovascular system**	B01A	Antithrombotic agents
		C01	Cardiac therapy
		C02	Antihypertensives
		C03	Diuretics
		C07	Betablocking agents
		C08 C09	Calcium channel blockers Agents acting on renin-angiotensin system
LIP	**Lipids**	C10	Lipid modifying agents
IS	**Immune system (allergy)**	D04A	Antipruritics, incl. antihistamines, anesthetics, etc.

		R06	Antihistamines for systemic use.
CNS	**Central Nervous system**	N05	Psycholeptics
		N06	Psychoanaleptics

2.2 Study area

9 Belgium is a 11 Mio inhabitants, densely populated, European country (374 inhab./km^2). It is divided into three administrative regions: Flanders in the North (tight urban network, densely inhabited), Wallonia in the South (greener, less densely populated, looser city network) and the Brussels Capital Region (BCR) in the center. The BCR corresponds to the urban core of the city of Brussels, while the urban agglomeration sprawls into both Flanders (in the Province of Vlaams-Brabant) and Wallonia (in the Province of Brabant Wallon). Belgium is divided into provinces (10 provinces + BCR) as illustrated in **Figure S1** in the Supplementary Material, and further into 589 municipalities at the date of the analysis. The municipality of Herstappe was removed from the analyses because of its small size (88 inhabitants in 2018) (StatBel, 2018).

10 The three Regions have their own political administration, language (Dutch in Flanders, French in Wallonia, German in the German-speaking community, and both Dutch and French in the BCR), and universities delivering medical degrees. Reimbursement criteria are defined at the national level, but regional factors may induce differences in practices.

2.3 Environmental and socio-economic variables

11 Our aim is not to statistically explain the spatial variation of medication consumption by a set of variables, but to look at their co-occurrence in a purely exploratory (descriptive) perspective. Hence, we gathered information on several standard environmental (ENV) and socio-economic (SE) characteristics at the level of the municipalities.

12 Data on air pollution were provided by the Belgian Interregional Environment Agency (Irceline, 2018) : data used in this study include average values of Particulate Matter 2.5 ($PM_{2.5}$), Particulate Matter 10 (PM10), Nitrogen Dioxide (NO2), and Black Carbon (BC) in 2015. These are measured in fixed monitoring stations and further modelled by $4 \cdot 4$ km cells. To link the air pollution data with the medication data, the pollutant concentrations were estimated at the municipality level.

13 Variables on green spaces were obtained from the Corine Land Cover dataset (European land-use dataset) developed by the European Environment Agency (Larsen, 2002). Green space is here defined as the sum of urban green, forests, pastures and agricultural land, and semi-natural areas. For this study we used the percentage of green spaces (hereafter noted "*Total GS*") in each municipality, and the average distance from the centroid of the built-up surface to the nearest green space (hereafter noted "*Ave Near GS*").

14 Standard socio-economic variables based on existing international literature (Steele *et al.*, 2007 ; Reiss, 2013 ; Mayer and Österle, 2015 ; Vanthomme and Gadeyne, 2019) were used as proxies for education, poverty, type of employment. For the purpose of our study, we used the share of unemployed persons in the 18–64-year-old population (noted *Unemployed*), the share of individuals aged 25-64 with primary education only (noted *Primary ed. 25-64y*), the share of individuals aged 25-64 with a higher education degree (noted *Higher ed. 25-64y*), the share of manual workers (noted *Manual workers*) and the share of foreign-born inhabitants coming from low income countries (noted *Foreign-born*). The Belgian Statistical Office (StatBel) provided data on median income and population density in 2014, while socio-economic variables were

derived from the latest Belgian Census (2001) as no other census was conducted since. The descriptive statistics about these variables are reported in **Table S1** in the Supplementary Material.

2.4 Methodology

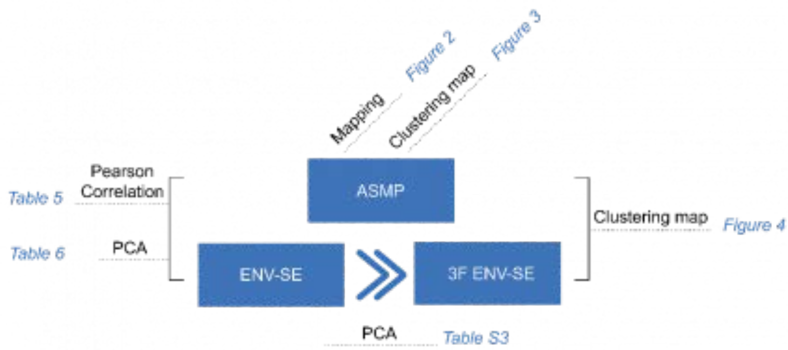
15 The five age-standardized medication reimbursement prevalence (ASMP) were first mapped at the municipality level. For all these maps, Jenks discretization was applied in order to minimize the intra-class and maximize the inter-class differences. The visual output of each map is accompanied by the computation of a Moran's *I* index for quantifying spatial autocorrelation. Spatial autocorrelation has been assessed considering all municipalities sharing at least one border (direct neighbors).

16 Correlations between all five ASMP variables were computed using Pearson coefficients (Table 5). A hierarchical clustering of the five ASMP variables was then computed using Ward's method to identify clusters of municipalities with similar medication reimbursement spatial patterns (Figure 3).

17 Pearson correlations were computed between all ASMP and ENV / SE variables (not reported here) and further summarized by a Principal Component Analysis (PCA) (see Table S2) as well as on the ENV and SE variables only (see Table S3). The PCA is here used as an exploratory tool aiming at simply reducing the size of the dataset in terms of variables : components are a linear combination of initial variables that co-vary spatially. PCA was therefore used in an exploratory way, to present which variables co-vary best and if they do. A Varimax rotation was applied. We limited ourselves to factors with *eigenvalues* >1. A Ward clustering is then performed following the PCA to present a spatial partition of Belgium in terms of the variables considered.

18 A summary of the data used, and the analysis carried out in the paper can be found in **Figure 1**.

Figure 1 : Schematic outline of analyses



3. Analysis and results

3.1 Mapping the Age-Standardised Medication reimbursement Prevalence

19 Basic descriptive statistics about the ASMP variables are reported in **Table 2**. Results for both men and women are presented separately. Since the gender difference is not significant (almost identical descriptive statistics and comparable medication reimbursement patterns - see correlation coefficients for each medication group between men and women noted *r* in Table 2), we further limit our report to men only (women data and results are not illustrated, but available upon request : statistical differences are very limited).

Table 2 : Descriptive statistics of the prevalence of the 5 groups of reimbursed medications (ASMP) in Belgium, by gender

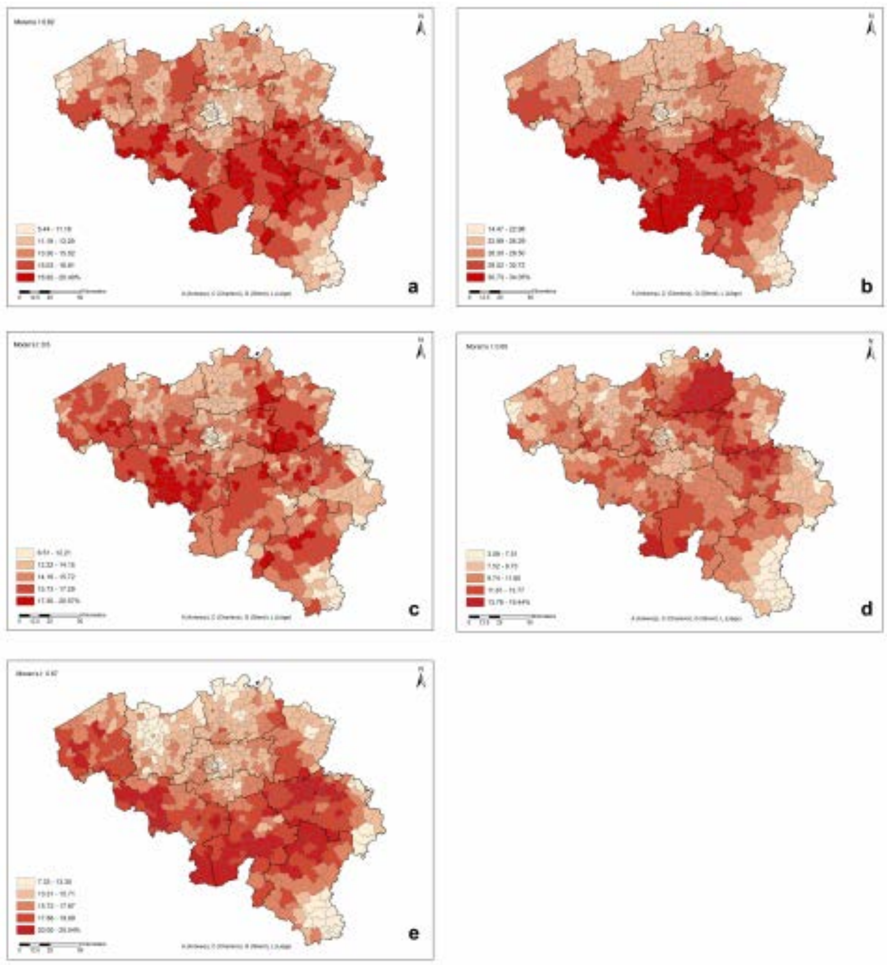
Medication Group	Gender	Mean	Std dev	Min	Max	*Median*	*r*
RS	*men*	14.23	2.33	5.44	20.4	14.09	0.95
	women	14.01	2.52	5.34	21.99	13.84	
CVS	*men*	27.64	2.87	14.47	34.09	27.6	0.95
	women	27.48	2.64	15.05	33.01	27.57	
LIP	*men*	15.26	1.85	6.51	20.57	15.43	0.86
	women	15.21	2.09	7.23	21.16	15.26	
IS	*men*	10.78	2.33	3.09	19.44	10.73	0.97
	women	10.67	2.12	2.84	19.61	10.51	
CNS	*men*	16.7	2.88	7.33	25.54	16.72	0.96
	women	16.83	2.75	8.01	23.59	16.66	

n= 588 Std dev : standard deviation, Min : minimum value, Max : maximum value, r : Pearson correlation coefficient between ASMP for men and ASMP for women for each medication group.

20 The 5 choropleth maps of the prevalence of medication reimbursement are reported in **Figure 2**. Contrary to our expectations, spatial structures look alike, except for *IS* which concerns mainly medications associated with allergies. Medication reimbursements for the immune system *IS* (Figure 2) are more prevalent in the North-East of the country and more particularly in the Province of Antwerp, and partially in the South-East near the border with France (South in the Province of Hainaut, and in the western part of the Province of Namur). The Province of Hainaut and Namur are both characterized by a high prevalence of medication reimbursements for the respiratory system (*RS* - Figure 2), the cardiovascular system (*CVS* – Figure 2), and the central nervous system (*CNS* - Figure 2), all expanding towards the East. Wallonia, with the exception of Walloon Brabant, is generally characterized by high prevalence of medication reimbursements, regardless of the type of ASMP. Brussels (BCR) tends to have lower values of most ASMP variables, whereas the eastern part of the province of Antwerp seems to concentrate medication purchase for allergic symptoms.

21 A Moran's I index is associated with each map. All five ASMP measures are characterized by a positive and significant autocorrelation, all varying between +0.50 and +0.67 : municipalities that look alike tend to be closely located.

Figure 2 : Spatial variations of ASMP, and Moran's I index, for the five medication groups, for men in 588 municipalities in Belgium between 2012 and 2014



a) medication for respiratory obstructive airway diseases such as asthma or COPD (RS) ; b) medication used to reduce blood pressure and to treat other cardiovascular problems like ischemic diseases (CVS) ; c) medication prescribed to reduce hyperlipidemia (LIP) ; d) medication to treat allergy symptoms (topic and systemic) (IS) ; e) drugs acting on the central nervous system (CNS).

3.2 Comparing ASMPs

22 The Pearson correlation coefficients between the five medication groups (**Table 3**) confirm the visual analyses: coefficients are positive and statistically significant. The strongest correlations are observed between the cardiovascular system medication group (*CVS*) and all other medication groups with the exception of the immune system (*IS*) targeted medications. From Figure 2 it is clear that *IS* has a different spatial structure, hardly explainable by common knowledge. The high concentration in the East of Antwerp may be due to the presence of a natural allergen or to polluted air emitted in and around Antwerp and pushed by western dominant winds. These hypotheses should be investigated and verified by further individual medical analyses and diagnoses.

23 High correlations between ASMPs can also be explained by multimorbidity and polypharmacy as recently discussed by Van Den Akker *et al.*, (2019) for Flanders.

Table 3 : Pearson correlation coefficients between the five groups of medications in Belgium

	RS	CVS	LIP	IS	CNS
CVS	**0.82**	1			
LIP	**0.54**	**0.71**	1		
IS	0.41	0.44	0.40	1	

CNS	**0.68**	**0.81**	**0.57**	0.39	1

All r are significant at 0.0001. n = 588 municipalities.

3.3 Clustering Belgian municipalities with the 5 ASMP variables

24 A Ward clustering method is applied on the 5 ASMP variables to obtain groups of municipalities that are similar in terms of medication reimbursement practices. Three clusters are optimally identified. Contrary to expectations, fragmentation is small: each cluster consists of contiguous municipalities, meaning that close municipalities have more similar ASMP profiles than distant ones (**Figure 3**). *Cluster 1* (in yellow) extends principally in the North of the country (Flanders), but also in the South-East in the province of Liège (including, among others, the German speaking Community of Belgium) and partly in the province of Luxembourg. Despite its location within Wallonia, most of the municipalities of the province of Brabant Wallon are also grouped into Cluster 1. C*luster 2* (green) mainly includes (1) municipalities in and around the Eastern and South-eastern part of Brussels, and (2) municipalities close to the border of Belgium and/or in the vicinity of an important international workplace (i.e. Luxembourg). Cluster 2 is characterized by the lowest values of the means (**Table 4**), suggesting low prescription prevalence in those municipalities and/or the purchase of medications in the neighboring country where they may be cheaper or more easily available. *Cluster 3* (in red) extends mainly in Wallonia, although it also includes a few municipalities scattered in Flanders. Cluster 3 is characterized by high means for each variable, pointing to higher prescription rates of medications, whatever the type.

Figure 3 : Composition of the clusters of the 5 ASMP.

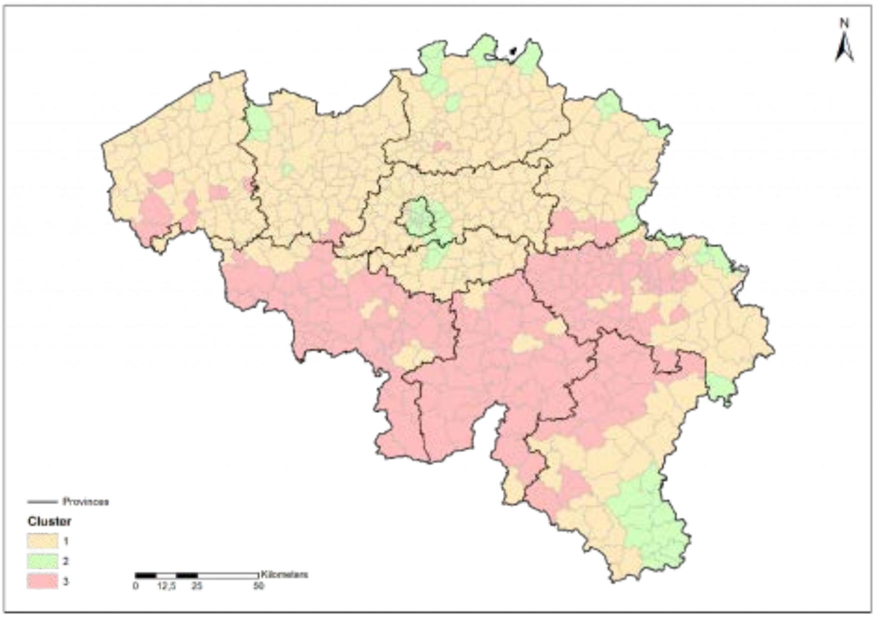


Table 4 : Cluster composition for the 5 ASMP variables (mean and standard deviation)

	Cluster 1 (*n*=361)	**Cluster 2** *(n =56)*	**Cluster 3** *(n =171)*
RS	13.68 (1.44)	10.27 (1.60)	16.68 (1.30)
CVS	27.05 (1.55)	22.15 (2.16)	30.67 (1.34)
LIP	15.24 (1.50)	12.21 (1.57)	16.28 (1.45)
IS	10.89 (2.35)	7.46 (1.66)	11.64 (1.32)

CNS	15.87 (1.97)	12.53 (1.84)	19.82 (1.48)

n refers to the number of municipalities included in cluster

3.4 Co-variation of ASMP and environmental / socio-economic variables

25 The thirteen environmental and socio-economic variables defined in Section 2.3 are now also taken into consideration. These variables are potentially related to the five ASMP variables as they are a priori assumed to play a (major) role in health issues (and hence medication consumption). Correlations are significant but not extremely high (see **Table 5**).

26 Most correlations between ENV variables and ASMP are negative with the exception of (1) the percentage of total green (*TotalGS*), meaning that the ASMP increases with greenness, which may appear as counter-intuitive but consistent with the North South divisions illustrated in the preceding maps, and is also consistent with recent research about childhood asthma (Aerts et al., 2020), and (2) between allergies and $PM_{2.5}$. In other words, medication reimbursements are poorly and negatively correlated to environmental variables: the higher the pollution, the smaller the ASMP values. This does not mean that pollution and health are not associated but that the spatial variations of the measures are little associated, at least if no control variable is considered.

27 Looking at SE variables, we observe that most ASMP variables are positively correlated to the proportion of unemployed, while central nervous system (*CNS*) and respiratory (*RS*) medication reimbursements are positively correlated to the share of population (25-64y) with primary education only. Strong negative correlations are to be found between the proportion of people with higher education (25-64y), and foreign born and most groups of medications (except for the immune system (*IS*), and central nervous system (*CNS*), respectively). Also, median income and population density both show a negative sign with asthma and chronic obstructive pulmonary disease (*RS*), and cardiovascular problems (*CVS*), and median income is also negatively correlated with depression and anxiety (*CNS*).

Table 5 : Pearson correlation coefficients between the five ASMP and the ENV (top rows) and SE variables (bottom rows)

	RS	*CVS*	*LIP*	*IS*	*CNS*
$PM_{2.5}$	-0.29***	-0.29***	n.s.	0.15***	-0.30***
PM_{10}	-0.20***	-0.19***	n.s.	0.12**	-0.22***
NO_2	-0.42***	-0.43***	-0.22***	n.s.	-0.29***
BC	-0.33***	-0.32***	-0.18***	n.s.	-0.23***
Total GS	0.32***	0.30***	0.16***	n.s.	0.14***
Ave near GS	-0.33***	-0.30***	-0.26***	-0.14***	-0.15***
Manual workers	n.s.	n.s.	0.18***	0.17***	n.s.
Unemployed	0.37***	0.41***	0.16***	n.s.	0.52***
Foreign-born	-0.28***	-0.29***	-0.28***	-0.19***	-0.08*
Primary ed. 25-64y	0.14***	n.s.	n.s.	-0.14***	0.11***
Higher ed. 25-64y	-0.34***	-0.35***	-0.29***	-0.16**	-0.32***
Median income	-0.26***	-0.50***	-0.10**	n.s.	-0.50***
Population density	-0.30***	-0.31***	-0.26**	-0.13**	-0.13**

*** : 0.001, ** : 0.01, n.s. : non significant

28 A PCA is first performed on all environmental (ENV), socio-economic (SE) and ASMP variables in order to see how they are related to each other at the municipal level within Belgium (see **Table S2** in Supplementary Material). Factors selected were limited to those with an eigenvalue greater than 1. Environmental, socio-economic and medication reimbursements are independent from each other. Environmental variables ($PM_{2.5}$, PM_{10}, NO_2, BC) have high positive loadings on *Factor 1* as well as the percentage of green space, which has a negative loading. *Factor 2* gathers socio-economic variables with high positive loadings on the share of unemployed, the share of foreigners born in low-income countries, population density and distance to the closest green space, while median income has a negative sign. *Factor 3* is composed of the five ASMP variables, confirming their specific and independent spatial structure. *Factor 4* gathers SE variables related to education (high proportion of low education, manual jobs; low proportion of high education). Several PCAs were also performed separately for the two Belgian Regions (Flanders and Wallonia). Given the geography of the country, Brussels Capital Region was included once in the Flemish Region, and once in the Walloon Region. Results (not illustrated here), confirm the independence of the three groups of variables (ASMP, ENV and SE) discussed above.

29 As previously mentioned, and as represented in Figure 1, an additional PCA was conducted on the thirteen ENV and SE variables (no ASMP variable included) in order to synthetize the environmental and socio-economic structure of the country into a few new variables and to further explore their link with the reimbursement prevalence. Three factors appear (**Table S3** in Supplementary Material). *Factor 1* is characterized by positive loadings on air pollution ($PM_{2.5}$, PM_{10}, NO_2, and BC), population density, distance to green spaces, and the proportion of individuals born in low-income countries and a negative loading on percentage of green areas. *Factor 2* is characterized by lower socio-economic characteristics: positive loadings on share of unemployed, presence of foreigners born in low-income countries, population density, and negative loadings with median income. *Factor 3* is composed of a high share of manual workers and share of population (25-64y) with a low education, and consequently a low share of population (25-64y) with higher education.

30 A second cluster analysis was then performed on the scores of these three factors as well as the five ASMP medication groups (see **Figure 4** and **Table 6**). The BCR with its better-off South/Southeastern periphery clearly pops up in *Cluster 3* (green), alongside with some border municipalities, close to Luxembourg and Germany. This cluster is characterized by low prevalence of reimbursement for all groups of medications, as well as a higher education level (Factor 3). *Cluster 4* (in red) mainly groups Walloon municipalities, with the exception of the Province of Brabant Wallon that clusters with the Northern part of the country. This red cluster is predominantly characterized by high reimbursement rates for medication associated with the respiratory system, the cardiovascular system, and the central nervous system. The Province of Brabant Wallon is part of *Cluster 1* (light blue). This cluster covers mainly the North of the country (Flemish Region), with some exceptions in the provinces of Liège and Luxembourg (around the green cluster). It is characterized by low prevalence of reimbursements for medications for the respiratory system and the central nervous system, a higher income, and low unemployment. The last cluster (*Cluster 2*, in orange) spreads primarily into two areas in the Flemish Region (West Vlaanderen and South-West Limburg/East of Antwerp). Cluster 2 is characterized by high medication prescriptions for the immune system and lipid-lowering medication, a lower share of higher educated people and more manual workers. Of note, South-West of Limburg was deeply hit by the Covid-19 (see Sciensano, 2019).

31 This last clustering confirms the strong and clear spatial structure observed in Figure 3. With some exceptions, clusters seem to follow, again, the linguistic/regional border between Flanders and Wallonia. Adding environmental and socio-economic variables does not change the trend.

Figure 4 : Clusters based on medication reimbursements (5 ASMP), and the 3 components (PCA scores) extracted from environmental and socio-economic variables.

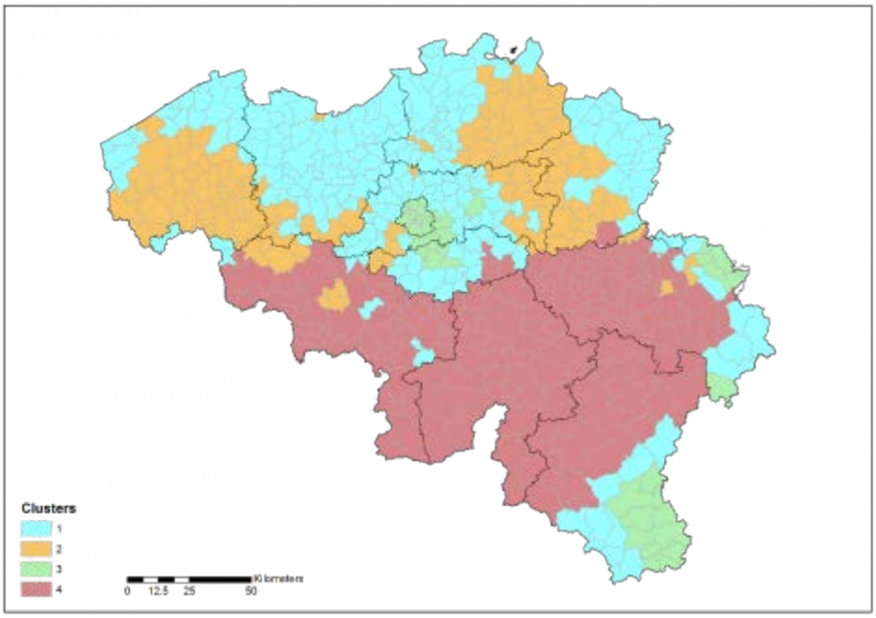


Table 6 : Cluster composition : mean and standard deviation of the five ASMP variables and three PCA factors

Variable	Cluster 1 (*n*=180)	Cluster 2 (*n* =144)	Cluster 3 (*n* *(n=55)*	Cluster 4 (*n* =209)
RS	13.18 (2.24)	13.89 (2.14)	10.17 (2.24)	16.43 (2.27)
CVS	26.18 (2.78)	27.58 (2.65)	22.07 (2.78)	30.39 (2.72)
LIP	14.45 (1.87)	15.96 (1.82)	12.18 (1.87)	16.27 (1.77)
IS	9.63 (2.38)	12.54 (2.31)	7.56 (2.38)	11.41 (2.08)
CNS	14.79 (2.86)	16.61 (2.77)	12.52 (2.86)	19.52 (2.92)
Factor 1 (high loadings on *PM2.5, PM10 NO2 and BC, Ave near green ;* low on *Total GS*)	0.24 (0.98)	0.31 (0.88)	0.68 (0.99)	-0.60 (0.76)
Factor 2 (high loadings on *Unemployment, Foreigners (LIC), Population density ;* low on *Median income*)	-0.33 (0.99)	-0.62 (1.00)	0.68 (1.00)	0.54 (0.82)
Factor 3 (high *Manual workers, Primary ed. 25-64y ;* low *Higher ed. 25-64y*)	-0.09 (1.02)	0.40 (1.05)	-0.86 (1.00)	0.03 (0.87)

4. Discussion and conclusion

32 We initially intended to use medication reimbursement data as a proxy for health. The Belgian sickness fund provided us data about medication prescriptions geocoded at the place of residence at municipality level. The exploratory spatial analyses conducted here show a very consistent spatial pattern, with a strong positive spatial covariation of the five types of medications, as well as their independence from environmental and

socio-economic characteristics. But this pattern questions the real meaning of the data provided.

33 The data used are based on medications reimbursed by the Belgian sickness funds. This information has intrinsic limitations: first, it does not include people not covered by the Belgian social security system. Nevertheless, the proportion of residents that are not covered is estimated to be very low (less than 2%), therefore the potential selection bias related to this limitation can be considered minimal. Second, non-reimbursable or not prescribed medications are not included, and the purchase and reimbursement of a medication does not equate its consumption. However, the information on medication purchase used here can be considered as a good indicator of the use of the Belgian health care system, as all purchased and reimbursed medication in Belgium are prescribed by a doctor. Medication is prescribed because of a diagnosis; hence, we can confidently assume that the practitioner of the patient buying the medication does consider that the person needs it. Last, the data does not provide information about the consumer (precise geo-location, and characteristics of the person), nor about the quantity of medication prescribed and bought yearly, nor about the exact pathology the drug was prescribed for, or its severity or chronicity. These biases are unfortunately not possible to estimate, nor to quantify. This database is originally built by and for health insurance companies; it is here diverted for potential health geography purposes in a specific multidisciplinary research project (GrespHealth), which aims at analyzing the relationship between health and green/blue environments.

34 We here used age-standardized data at the municipality level. This level of spatial aggregation has the advantage of having a very low number of missing data, it avoids privacy issues and allows comparison with other contextual variables, but it does not allow any in-depth analysis at the individual level, which would have been desirable for causal analysis (see e.g. Kwan, 2009 ; Park and Kwan, 2017). Aggregating data entails indeed possible modifiable areal unit problems (see e.g. Openshaw and Taylor, 1979 ; Dusek, 2004) and/or ecological fallacy errors, that is, inferring about individuals on the basis of spatially aggregated data (see e.g. Openshaw, 1984 ; Wakefield and Lyons, 2010). In statistical analysis, spatial is special. Here, analyzing spatial variations at the level of all municipalities of one country allows identification of regional structures and to question the role of the linguistic/political border, and is relevant in terms of public health in Belgium. However, it is impossible to disentangle the different components such as medical doctors' education and practice, medication purchase, pharmaceutical sales promotion, role of commercials, for which individual data would be essential. To our knowledge, few studies have analyzed these variations in space as such. Waldhoer et al. (2008) looked at the spatial distribution of infant mortality in Austria for different causes of death. They found a clear non-random spatial distribution of mortality causes, and a non-relevant effect of socio-economic status of the mother. Moreover, this paper also reminds how representing a country (Belgium) by some selected observations in one part of the country (Tyrstrup et al., 2017) may lead to very questionable and false results. Tyrstrup et al. (2017) in fact take one region of Belgium (Flanders) as representative of the whole country on an international scale comparison with the Netherlands and Sweden.

35 Last but not least, environmental and socio-economic variables are not straightforward to measure and far from being perfect here. Averaging pollutants such as BC and NO_2 at the municipality level introduces estimation biases (they are measured punctually, interpolated on a grid and aggregated by municipalities that are irregular in shape and size).

36 The sign and value of the correlation coefficients between the five medication groups fit with medical knowledge. The cardiovascular medication group included in our study is not only prescribed to treat diseases but, like the lipid modifying agents, it is also prescribed to prevent the onset of chronic cardiovascular diseases or acute events. The respiratory medication is mainly used to treat symptoms of asthma (childhood and early adulthood) and chronic obstructive pulmonary disease (COPD) (adulthood and elderly). Since COPD shares many risk factors with cardiovascular diseases, it was expected that COPD medication sales (and reimbursement) would be strongly correlated with those of cardiovascular medication. Finally, the strong correlation

observed between medication reimbursement for the central nervous system (mainly used among patients with mood disorders) and cardiovascular system medication sales, is consistent with the increasing evidence that mental health problems may be risk factors for cardiovascular disease (Cohen, Edmondson and Kronish, 2015).

37 Clustering the medication reimbursements for the five medication groups shows a clear spatial pattern. The regional (and linguistic) division appears clearly, as well as the effect of the international borders (with Luxembourg in particular), together with the possible effect of the presence of expats with special status in the Region of Brussels. In addition, medication reimbursement prevalence is generally higher in the southern part of the country, a region characterized by lower pollution levels, and a high share of green spaces. Low prevalence of medication reimbursement can also be found in the big cities, hence presenting an urban-rural difference in purchase and reimbursement. All medication reimbursement types are highly autocorrelated (Moran's I ≥ 0.5). Consistently, this structure cannot be explained by environmental factors, which are not affected by the administrative partition, but it is suggestive of an effect of prescription practices. We included in this study a selection of environmental and socio-economic variables in addition to the medication reimbursement data to better understand the spatial variations in medication prescription. We computed Pearson correlations among ASMP variables and the environmental and socio-economic ones. This yielded unexpected inverse correlations with air pollution ($PM_{2.5}$, PM_{10}, NO_2, and BC) and distance to green spaces, while the correlation was positive with the share of green spaces. These results are contrary to the existing literature based on individual studies indicating the adverse effect of air pollution on health, and the beneficial effects of a natural environment (Pereira *et al.*, 2012 ; Sofianopoulou *et al.*, 2014 ; Triguero-Mas *et al.*, 2015 ; Landrigan *et al.*, 2017 ; Thurston *et al.*, 2017), suggesting potential ecological fallacy in our study when looking at the correlation with environmental factors. On the contrary, our results regarding socio-economic position are in line with results of previous research (see e.g. Bossuyt et al., 2004 ; Renard et al., 2019). We observe that low socio-economic position (share of unemployed, manual workers, young people with primary education only) is positively correlated with prevalence of medication reimbursement, with the exception of individuals coming from low-income countries.

38 Principal Component Analysis including medication reimbursement data, environmental and socio-economic variables indicates that there is no relationship between the prevalence of medication reimbursements and all other collected variables, confirming again the strong independency of such variables. The clustering analysis, including the five medication reimbursement groups and the three PCA factors computed on the environmental and socio-economic variables, presents a strong spatial structure. The addition of environmental and socio-economic variables does not have a relevant impact on the spatial pattern of medication reimbursements, as ASMP appear to be highly correlated between each other and independent from external factors.

39 The patterns of medication reimbursement in Belgium highlighted in this paper indicate that the lack of information at the individual level does not really allow us to measure health, and to draw conclusions on the effects of factors such as environmental characteristics or socio-economic position on wellbeing. Our data rather hints at medical and pharmaceutical practices and reminds us to keep in mind the existence of geographical differences in medical practice when using prescribed medication as a proxy for disease. Information on the education and training of the medical doctors and their current working location might be useful to further understand medication reimbursements distribution in Belgium. Moreover, "commercial" practices of pharmaceutical firms would be an interesting issue to understand further, especially in a country like Belgium divided by a linguistic border.

40 As a conclusion, this paper describes the spatial intra-national variations of medication prescriptions in Belgium. The use of data for an entire country and for several medication groups allows to generate hypotheses on the factors leading to medications purchase in Belgium for all age groups. The study suggests that medication prescription and reimbursement is not (only) an environmentally driven problem, at

least at the level of the municipalities. Variation in medication prescription and reimbursement may be linked to curative healthcare matters and language/education of practitioners. Therefore, it is important to be careful when using and interpreting such data as health proxies: this paper reminds us how important it is to describe, control and understand the data before moving into more explanatory analyses.

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Supplementary Material

Figure S1 Administrative partition of Belgium in provinces.

West-Vlaanderen, Oost-Vlaanderen, Antwerp, Vlaams-Brabant, Limburg, correspond to in Flanders ; Hainaut, Brabant Wallon, Liège, Namur, Luxembourg, correspond to Wallonia. BCR = Brussels Capital Region. G = Gent, A = Antwerp, C = Charleroi, L = Liège.

Table S1 Descriptive statistics of the ENV and SE variables

	Units	Mean	Std Dev	Min	Max	Median	95th Percentile
$PM_{2.5}$	µg/m3	10.73	1.80	4.45	14.41	11.13	13.22
PM_{10}	µg/m3	16.47	2.96	5.81	22.55	17.23	20.40
NO_2	µg/m3	0.89	0.22	0.42	2.28	0.86	1.23
BC	µg/m3	14.50	5.08	5.25	38.42	13.94	23.71
Manual Workers	%	9.81	3.06	1.94	17.62	9.40	14.86
Unemployed	%	9.55	5.40	2.87	33.90	8.22	21.50
Foreigners (LIC)	%	2.46	3.28	0.22	36.72	1.62	7.07
Primary ed. 25-64y	%	14.49	4.21	5.11	33.20	14.29	21.56
Higher ed. 25-64y	%	28.32	8.53	10.20	65.22	26.39	45.25
Median Income	Euros (€)	24967	2721.93	14998	34229	25386	28744.40
Population Density	Inhab./km2	767.80	2134.82	24.80	24027.90	305.90	1972.97
Ave near GS	Meters	137.40	115.60	21.78	1132.00	110.82	285.84
Total GS	% land	72.56	19.68	0	98.54	76.80	95.36

Statistics computed on all Belgian municipalities, at the exception of Herstappe (n=588).

Table S2 Loadings of the Principal Component Analysis conducted on the ASMP, ENV and SE variables.

Variable	Factor 1	Factor 2	Factor 3	Factor 4
$PM_{2.5}$	**0.92**	-0.23	.-0.05	0.06
	0.90	-0.18	0.04	0.05

PM_{10}				
NO_2	**0.86**	0.22	-0.25	0.09
BC	**0.89**	0.25	-0.12	-0.22
% Manual Workers	0.100.02	-0.43	0.02	**0.83**
% Unemployed	-0.14	**0.84**	0.36	-0.02
% Foreigners (LIC)	0.42	**0.77**	-0.26	-0.15
% Primary ed. 25-64y	0.03	0.34	0.01	**0.87**
% Higher ed. 25-64y	0.18	-0.07	-0.27	**-0.90**
Median Income	0.12	**-0.86**	-0.23	-0.24
Population Density	**0.53**	**0.67**	-0.26	-0.03
Ave near GS	0.45	**0.55**	-0.30	-0.03
% Green Spaces	**-0.80**	-0.39	0.11	0.15
RS	-0.28	0.06	**0.81**	0.10
CVS	-0.26	0.08	**0.90**	-0.04
LIP	-0.01	-0.12	**0.80**	0.10
IS	0.22	-0.18	**0.66**	0.05
CNS	-0.22	0.31	**0.82**	0.05

Loadings > 0.5 are in bold ; loadings < 0.1 are in grey and are not significant.

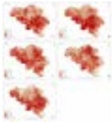
Table S3 Loadings of the PCA conducted on ENV and SE variables.

Variable	Factor 1	Factor 2	Factor 3
$PM_{2.5}$	**0.88**	-0.34	0.09
PM_{10}	**0.85**	-0.30	0.09
NO_2	**0.91**	0.11	0.07
BC	**0.92**	0.12	-0.21
% Manual Workers	0.05	-0.42	**0.83**
% Unemployed	-0.10	**0.87**	-0.03
% Foreigners (LIC)	**0.56**	**0.70**	-0.20
% Primary ed. 25-64y	0.08	0.36	**0.86**
% Higher ed. 25-64y	0.22	-0.12	**-0.93**
Median Income	0.06	**-0.85**	-0.34
Population Density	**0.66**	**0.58**	-0.08
Ave near GS	**0.57**	0.47	-0.09
Total GS	**-0.84**	-0.28	0.15

Loadings > 0.5 are in bold ; loadings < 0.1 are in grey and are not significant.

Table des illustrations

Titre	Figure 1 : Schematic outline of analyses
URL	http://journals.openedition.org.proxy.bib.ucl.ac.be/cybergeo/docannexe/image/36950/img-1.png
Fichier	image/png, 20k
Titre	Figure 2 : Spatial variations of ASMP, and Moran's I index, for the five medication groups, for men in 588 municipalities in Belgium between 2012 and 2014
Légende	a) medication for respiratory obstructive airway diseases such as asthma or COPD (RS) ;

		b) medication used to reduce blood pressure and to treat other cardiovascular problems like ischemic diseases (CVS) ; c) medication prescribed to reduce hyperlipidemia (LIP) ; d) medication to treat allergy symptoms (topic and systemic) (IS) ; e) drugs acting on the central nervous system (CNS).
	URL	http://journals.openedition.org.proxy.bib.ucl.ac.be/cybergeo/docannexe/image/36950/img-2.png
	Fichier	image/png, 1,0M
	Titre	Figure 3 : Composition of the clusters of the 5 ASMP.
	**URL**	http://journals.openedition.org.proxy.bib.ucl.ac.be/cybergeo/docannexe/image/36950/img-3.png
	Fichier	image/png, 237k
	**Titre**	Figure 4 : Clusters based on medication reimbursements (5 ASMP), and the 3 components (PCA scores) extracted from environmental and socio-economic variables.
	URL	http://journals.openedition.org.proxy.bib.ucl.ac.be/cybergeo/docannexe/image/36950/img-4.png
	Fichier	image/png, 294k
	Titre	Figure S1 Administrative partition of Belgium in provinces.
	**Légende**	West-Vlaanderen, Oost-Vlaanderen, Antwerp, Vlaams-Brabant, Limburg, correspond to in Flanders ; Hainaut, Brabant Wallon, Liège, Namur, Luxembourg, correspond to Wallonia. BCR = Brussels Capital Region. G = Gent, A = Antwerp, C = Charleroi, L = Liège.
	URL	http://journals.openedition.org.proxy.bib.ucl.ac.be/cybergeo/docannexe/image/36950/img-5.png
	Fichier	image/png, 79k

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Référence électronique

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