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Dinneweth, Janna; Gadeyne, Sylvie

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La mortalité selon les causes de décès : approches spatio-temporelles

Unravelling the Evolution of Neurodegenerative Disease Mortality: Insights from 50 Years of Belgian Data

Démêler l'évolution de la mortalité liée aux maladies neurodégénératives: perspectives à partir de 50 ans de données belges

JANNA DINNEWETH ET SYLVIE GADEYNE

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Résumés

English Français

Neurodegenerative diseases (NDDs) are an increasingly pressing public health concern. This study investigates spatiotemporal variations in NDD mortality, focusing on dementias and Parkinson's Disease (PD) in Belgium from 1970 to 2020. Age-standardized mortality rates for the population aged 45 or older were calculated using indirect standardization methods, referencing 1970 rates and averaging deaths over 3 year-periods for stability. Spatial representations were created using mapping techniques. Moran's I tests assessed spatial autocorrelation. The findings reveal shifts in dementia classifications, with Alzheimer's Disease (AD) superseding dementia from 1980 to 1993, and later, dementia-related deaths surpassing AD deaths. Spatially, dementia ICD-codes clustered in Flanders while AD codes clustered in the Walloon region. PD-related deaths doubled from 1997 to 2020, with a shift from higher female proportions before 2004 to increased male rates from 2004 to 2020. Spatial analysis shows a notable rise in PD mortality rates in the Walloon region by 2000, yet a contrasting pattern was found in 2019. More research is needed to explore other explanatory factors for spatial variations beyond registration practices.

Les maladies neurodégénératives constituent une préoccupation croissante en matière de santé publique. Cette étude examine les variations spatio-temporelles de la mortalité liée aux maladies neurodégénératives, en se concentrant sur les démences et la maladie de Parkinson (PD) en Belgique de 1970 à 2020. Les taux de mortalité standardisés par âge pour la population âgée de 45 ans ou plus ont été calculés à l'aide de méthodes de standardisation indirecte, en référence aux taux de 1970 et en faisant la moyenne des décès sur des périodes de 3 ans pour assurer la stabilité. Des représentations spatiales ont été créées à l'aide de techniques de cartographie. Les tests de



l'indice de Moran ont évalué l'autocorrélation spatiale. Les résultats révèlent des changements dans les classifications des démences, l'Alzheimer prenant le pas sur la démence de 1980 à 1993, puis les décès liés à la démence dépassant ceux de l'Alzheimer. Spatialement, les codes ICD des démences étaient regroupés en Flandre, tandis que les codes de l'Alzheimer étaient regroupés dans la région wallonne. Les décès liés à la PD ont doublé de 1997 à 2020, avec un passage de proportions plus élevées chez les femmes avant 2004 à des taux accrus chez les hommes de 2004 à 2020. L'analyse spatiale montre une augmentation notable des taux de mortalité liés à la PD dans la région wallonne en 2000, mais un motif contrastant a été trouvé en 2019. Des recherches supplémentaires sont nécessaires pour explorer d'autres facteurs explicatifs des variations spatiales au-delà des pratiques d'enregistrement.

Entrées d'index

Mots-clés : mortalité, Belgique, 1970-2020, démence, maladie d'Alzheimer, maladie de Parkinson, pratiques d'enregistrement

Keywords: mortality, Belgium, 1970-2020, dementia, Alzheimer's disease, Parkinson's disease, registration practices

Texte intégral

1. Introduction

- 1 The global fertility and mortality decline have given rise to aging societies, a demographic shift with profound implications. The Gompertzian hypothesis posits that as individuals experience extended lifespans, they develop age-related diseases hardly apparent in earlier life stages. This has precipitated a growing concern regarding the burden of neurodegenerative diseases (NDDs) worldwide [Gitler et al., 2017; WHO, 2021]. NDDs encompass a spectrum of conditions, characterized by the gradual and progressive loss of neural cells, leading to impairments across cognitive, behavioural, and motor domains [Brown et al., 2005]. Among NDDs, all-cause dementia stands out as the predominant manifestation, with Alzheimer's disease (AD) being responsible for 60-70% of dementia cases globally [WHO, 2017]. Other notable forms of dementia include vascular dementia, dementia with Lewy bodies, and frontotemporal dementia. Following AD, Parkinson's disease (PD) emerges as the second most common NDD [Ascherio & Schwarzschild, 2016].
- 2 The primary objective of this study is to explore the spatial variations in NDD mortality in Belgium, with a specific focus on the major NDDs all-cause dementia and PD, spanning the period from 1970 to 2020. Despite Belgium's longstanding tradition of studying spatial differences in mortality [Van Rossem et al., 2018], and the prominence of dementias as a leading cause of death in the country [Sciensano, 2022], a comprehensive overview of spatial variations in NDD mortality is lacking. Noteworthy spatial variations in NDD mortality have been observed in European countries. For example, in France, dementia mortality rates were higher in five regions in the North East of the country [Brosselin et al., 2010]. In England, the highest dementia mortality was observed in the North East, South Central and South West [Watson et al., 2021]. In the case of PD, higher mortality rates were noted in the northern half of Spain [Pedro-Cuesta et al., 2009; Santurtún et al., 2016] and in North-West and Central Italy [Ulivelli et al., 2022].
- 3 This study is primarily descriptive and exploratory. To provide context for the observed patterns of NDD mortality, we discuss potential hypotheses, even though these aspects were not directly analysed in the text. For example, suggested explanatory variables for spatial variations include environmental pollutants. Compelling evidence suggests a connection between pesticide exposure and Parkinson's disease risk [Ascherio & Schwarzschild, 2016]. Similarly, there is a growing body of evidence linking air pollution to dementia risk [Killin et al., 2016]. Other explanatory variables include

socioeconomic indicators such as educational level and income, which have shown to be associated with NDD mortality in Belgium at the individual level [Dinneweth & Gadeyne, 2024]. At an aggregated level, mortality among people living with dementia was found higher in the most deprived areas of England [Watson et al., 2021]. Lastly, differences in registration practices have been noted as a contributing factor. Dementia mortality was higher in French regions with a high number of specialized memory clinics, suggesting better diagnosis [Brosselin et al., 2010]. Moreover studies from the United States [Akushevich et al., 2021; Lanska, 1997], and Australia [Jorm et al., 1989] have shown geographical variation in the tendency to report NDDs as contributing causes of death.

- 4 While these existing studies have contributed valuable insights into NDD mortality, none have undertaken an examination spanning a period longer than a decade. Consequently, this study aims to be a pioneering effort, comprehensively exploring spatiotemporal variations in NDD mortality over an extensive five-decade timeframe in Belgium. Prior to exploring the spatial patterns of NDDs, we will provide a brief historical overview of the investigated diseases and some background on the Belgian context.

2. A brief historical overview of dementia and Alzheimer's disease

- 5 The earliest accounts of age-related cognitive decline dates back to Pythagoras, who observed that in the second epoch of old age (beginning of the 81st life year), mortal existence closes, returning the system to the imbecility of infancy [Jameson, 1811, pp. 129-130]. Ancient Greek society faced challenges to legal competency during cognitive decline, as noted by Solon, who highlighted impairments in judgement due to “pain, violence, drugs, old age or the persuasion of a woman” [Freeman, 1926, pp. 114-115]. Hippocrates, considered the father of medicine, attributed cognitive decline to imbalances in bodily humors, viewing it as an inevitable outcome of aging. Plato and Aristotle similarly linked cognitive decline to old age, with Aristotle associating it with the accumulation of black bile [Papavramidou, 2018]. In contrast, Cicero argued against the inherent connection between aging and mental changes [Boller & Forbes, 1998]. He proposed that an active mental life could prevent cognitive decline in old age [Berchtold & Cotman, 1998], a concept central to the topical cognitive reserve hypothesis. However, Cicero's influence waned, overshadowed by other views in the Hellenistic Empire. For instance, Galen systemized medical knowledge, including “morosis” as a mental disorder characterized by intellectual dullness or deficiency, particularly in old age [Berchtold & Cotman, 1998]
- 6 In the 17th century, dementia saw more precise behavioural descriptions, leading to distinct conceptualizations. With increased tolerance for human body dissection, a trend emerged in exploring physiological changes in the brain underlying mental disorders. Thomas Willis, personal physician to King Charles II, introduced a dementia classification in his work “London Practice of Physick,” acknowledging age-related mental decline and identifying various causes. By the 18th century, brain examination expanded to pathologists, with William Cullen categorizing senile dementia as “amentia senilis,” defining it as the decay of perception in memory during old age. [Berchtold & Cotman, 1998]
- 7 In the early 19th century, pivotal advances in understanding senile dementia were spearheaded by French physician Philippe Pinel. Pinel advocated for compassionate mental illness care institutions, and his student Jean Etienne Esquirol introduced a revised classification system in 1838. Esquirol's work included detailed descriptions of mental disorders, distinguishing senile dementia from idiocy based on the loss of mental faculties due to disease. Building on Pinel and Esquirol's foundation, Belgian alienist Joseph Guislain linked dementia to cognitive disorders [Caixeta et al., 2014].

However Guislain did not adopt Esquirol's distinction between dementia and idiocy [Guislain, 1852, pp. 308-309]. This might be the reason why, in Belgium's first classification of causes of death in 1867, dementia and idiocy were still classified together as a single disease. Anatomists in the late 19th century scrutinized brain abnormalities, with Samuel Wilks attributing brain atrophy to dementia, while Otto Binswanger described vascular dementia caused by arteriosclerotic demyelination. [Berchtold & Cotman, 1998; Grand & Feldman, 2007]

8 In 1888, Alois Alzheimer earned his medical degree and joined the Municipal Asylum for the Mentally Ill and Epileptics in Frankfurt-am-Main. Collaborating with Franz Nissl, they aimed to advance psychiatry through detailed brain analysis, focusing on the cerebral cortex. In 1901, Alzheimer admitted Auguste Deter, a 51-year-old patient with severe memory loss and irrational fears. Using Max Bielschowsky's staining methods, Alzheimer identified neurofibrillary tangles and plaques in Auguste's brain. The unique presentation challenged existing diagnostic patterns, leading to the recognition of Alzheimer's condition as a distinct disease entity. Emil Kraepelin officially named it "Alzheimer's disease" in 1910, distinguishing it from senile dementia [Goedert & Ghetti, 2007]. This distinction between AD and senile dementia remained dominant until the 1970s [Assal, 2019]. In 1970, Tomlinson, Blessed, and Roth linked Alzheimer's neurofibrillary degeneration to dementia appearing after the age of 65. Consequently, AD shifted from a rare disease until the 1970s to an epidemic, attracting the majority of the diagnoses with a neurodegenerative condition [Vatanabe et al., 2020].

9 In recent years, dementia research has made significant progress in two key areas: diagnosis and the development of novel treatments. Biomarkers have played a pivotal role in enhancing diagnostic accuracy and monitoring disease progression. Concurrently, researchers are exploring new therapeutic modalities to slow down advancement and enhance the well-being of people affected by the disease. A noteworthy breakthrough in AD treatment strategies is the approval of Leqembi by the United States Food and Drug Administration in 2023. Leqembi, an anti-amyloid therapy, aims to reduce the buildup of amyloid-beta plaques in the brain. Despite these promising advancements, it is important to acknowledge that dementia remains without a cure. The intricate nature of dementia, with its multifaceted causes and varied clinical presentations, poses significant hurdles to developing interventions capable of halting or reversing the underlying neurodegenerative processes. [Maheshwari & Singh, 2024]

3. A brief historical overview of Parkinson's disease

10 Galen is credited with first identifying resting and intentional tremors in his work "*De tremore, Palpitatione, Convulsione et Rigore*" in 169 BC. Leonardo da Vinci later provided a detailed description of the shaking palsy, combining difficulty with voluntary movement and tremor [Li & Le, 2017]. Despite ancient literature offering general descriptions covering most PD symptoms, it was James Parkinson who medically described it as a neurological syndrome in "An Essay on the Shaking Palsy" in 1817 [Goetz, 2011]. Parkinson characterized shaking palsy (paralysis agitans) as "*Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forward, and to pass from a walking to a running pace: the senses and intellects being uninjured*" [Parkinson, 1817].

11 Jean-Martin Charcot, over 50 years later, was the first to use the term "Parkinson's disease" and differentiated it from other tremorous disorders. He rejected the earlier designations of paralysis agitans or shaking palsy, noting that PD patients are not necessarily weak and may not have tremors [Lanska, 2009]. William Gowers contributed a valuable study of PD demographics in the 1880s, amongst other

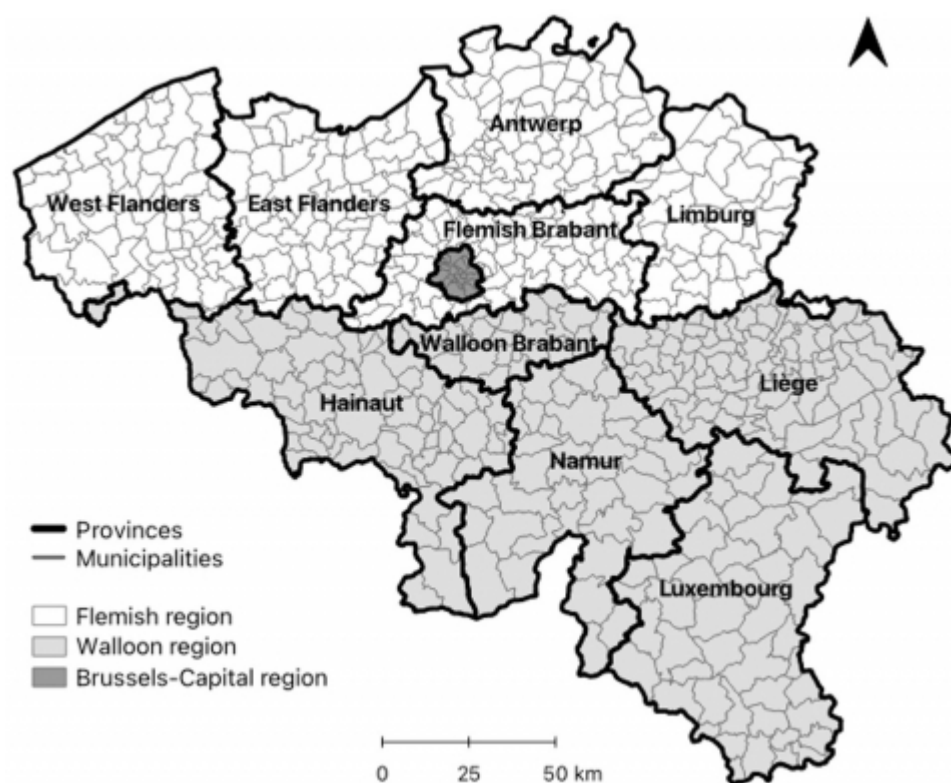
identifying the male predominance of the disorder [Goetz, 2011]. Édouard Brissaud, in 1899, suggested that PD originated pathologically from the damaged substantia nigra. By 1912, Frederick Lewy observed aggregated inclusions later identified as Lewy bodies by Konstantin Tretiakoff in 1919, all located inside the substantia nigra [Li & Le, 2017].

- 12 PD historically stood out among NDDs due to the availability of effective therapy based on dopamine replacement [Siderowf & Stern, 2003]. In 1960, Ehringer and Hornykiewicz demonstrated a severe reduction in dopamine concentration in the brains (striatum) of PD patients. Building on this, Hornykiewicz collaborated with Birkmayer in 1961 to administer intravenous levodopa to parkinsonian patients, introducing Larodopa (levodopa) worldwide in 1970 as the first effective anti-PD drug. Since the discovery of levodopa, various dopamine agonists have been developed and clinically used. Other advancements include the introduction of deep brain stimulation for treating PD tremors and cell-based therapy. Although these breakthroughs have helped our understanding of PD and suppress important symptoms, there is still no cure for PD. Recent efforts suggest a combination of environmental and genetic factors may contribute to PD development. [Goldman & Goetz, 2007; Li & Le, 2017]

4. The Belgian context

- 13 Belgium gained independence in 1830 and transitioned to a federal structure between 1970 and 1993. The country's administrative landscape is characterized by its complexity. This article outlines 3 administrative levels (Figure 1): regions, provinces, and municipalities (or communes). Belgium is divided into 3 regions, consisting of 10 provinces and 581 municipalities. Flanders, the Flemish region, comprises 300 municipalities distributed across 5 provinces: Antwerp, East Flanders, Flemish Brabant, Limburg, and West Flanders. The Walloon region encompasses 262 municipalities spread over 5 provinces: Hainaut, Liège, Luxembourg, Namur, and Walloon Brabant. The Brussels-Capital Region consists of 19 municipalities. [Belgian Federal Government, 2024]

Figure 1 Belgian regions, provinces, and municipalities



Source: Map constructed by author

- 14 After the Second World War, life expectancy at older ages has shown a significant increase in Belgium [Devos et al., 2010]. Eggerickx et al. [2020] reported a continuous upward trend in life expectancy at the age of 65, particularly for women who gained 8 years between 1945 and 2015 at this age. Men experienced a delayed increase, with life expectancy at 65 rising by 5 years from 1980 to 2015. A similar pattern was observed at the age of 80, with women's life expectancy increasing by 4 years from 1970 to 2015, and men's life expectancy increasing by 2-years during the same period. Since the 1990s, the gender gap in life expectancy has narrowed, possibly due to converging lifestyles, with men adopting more preventative behaviours and women adopting less health-favourable ones. [Eggerickx et al., 2020]
- 15 Despite this remarkable rise in life expectancy, not all parts of the Belgian population have benefited equally. For at least two centuries, a regional contrast has existed between Flanders in the north of the country and the Walloon region in the south. In the nineteenth century, mortality rates were higher in Flanders compared to the Walloon region. After the First World War, a reversal in this pattern began, unfolding at varying times for different ages and sexes. The reversal initiated with men and then extended to women. Among different age groups, the reversal initially affected older individuals before extending to younger ones. Since the early 1960s, the Walloon region has consistently exhibited higher mortality rates, resulting in life expectancy differences of 2.9 years for men and 2 years for women during the period of 2011-2015. [Eggerickx et al., 2020]
- 16 These mortality variations are intricately linked to socioeconomic distinctions between Flanders and the Walloon region [Deboosere & Gadeyne, 2002]. Both individual socioeconomic position and area-level socioeconomic characteristics are associated with higher mortality levels in Belgium [Van Hemelrijck et al., 2016]. However, even after controlling for socioeconomic variables, disparities persist at the regional and subregional levels, suggesting a more complex process contributing to geographical mortality differences [Deboosere & Gadeyne, 2002; Van Hemelrijck et al., 2016]. Other factors, such as environmental and cultural, may also play a significant role [Deboosere & Gadeyne, 2002].

5. Methods

- 17 The analysis is based on cause-specific mortality data spanning the years 1970 to 2020, sourced from Statistics Belgium¹. These individual-level records cover all individuals officially residing in Belgium and were aggregated to the municipal level, using the 2020 municipality borders. We utilized the spatial scale of the municipality as it represents the smallest scale available across all time periods studied, allowing for the observation of fine patterns in NDD mortality. Despite its small size, the municipality scale provides clear and concise maps. The population size and structure were derived from the Belgian censuses conducted in 1970, 1991, 2001, 2011, and register data from 2018. Our focus centred on two prominent NDDs: dementias and PD. The International Classifications of Disease (ICD) codes used for dementias and PD in ICD 8-10 are given in table 1.

Table 1 Number of deaths in Belgium (1970-2020) with dementia or PD diagnoses coded according to ICD, revisions 8 (1970-1978), 9 (1979-1995), and 10 (1996-2020)

	Diagnosis	N
Dementia		
ICD-8	290 Senile and presenile dementia	7,828
ICD-9	290 Senile and presenile dementia	10,701
	331 Other cerebral degenerations (including Alzheimer's disease)	24,109
ICD-10	F00-F03 Dementia	82,515
	G30 Alzheimer's disease	48,481
Parkinson's disease		
ICD-8	342 Paralysis agitans	4,616
ICD-9	332 Parkinson's disease	7,969
ICD-10	G20 Parkinson's disease	21,321

N = number of deaths

Source: Statistics Belgium

18 To explore the geographic patterns of NDD mortality in Belgium, we calculated age-standardized mortality rates for the population aged 45 years or older at the municipal level. In the light of the small size of certain municipalities, we opted for the indirect standardization method. More specifically, to standardize for age, we utilized the age-specific mortality rates of the entire Belgium population in 1970 as the reference standard. Recognizing the fluctuations and the small number of deaths in some municipalities, we used the average deaths over 3-year periods. This approach aimed to provide a more stable and representative basis for analysis. To ensure reliability of our findings, we conducted sensitivity analyses by using an alternative reference standard. Additionally, we also mapped the percentage share of NDD deaths to overall mortality by municipality. The results of both sensitivity analyses – presented in the supplementary materials (S1 & S2) – are very similar to the initial findings, suggesting no significant impact of the age-standardization on our results.

19 Subsequently, we transformed these mortality rates into spatial representations using mapping techniques for the periods 1969-1971, 1989-1991, 2000-2002, 2009-2011, and 2017-2019. We opted for the 2017-2019 timeframe instead of the 2019-2021 period, considering the potential impact of COVID-19 on the results. To evaluate the presence and significance of spatial autocorrelation, Moran's I tests were conducted. Moran's I ranges from -1 to 1, where positive values indicate positive spatial autocorrelation (similar values are spatially close to each other), negative values indicate negative spatial autocorrelation (dissimilar values are spatially close to each other), and values close to zero suggest spatial randomness. To calculate the Moran's I, we used a weights matrix based on distance proximity. The analyses were performed using open-source software, with QGIS 3.32 employed for spatial representation and R 4.3.0 for statistical analyses.

6. Results

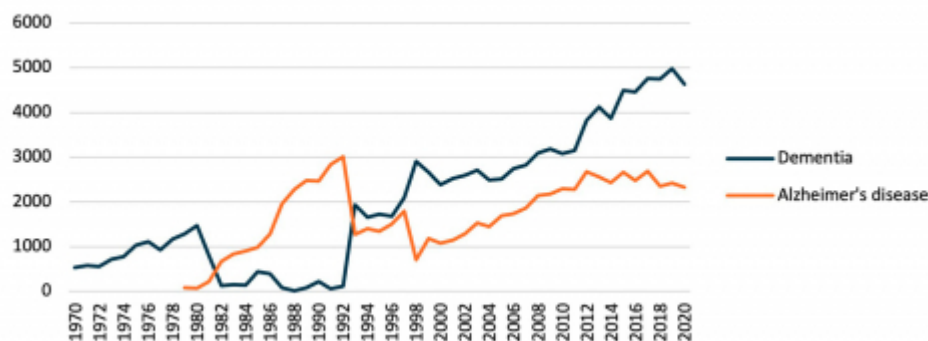
20 In this results section, we initially focus on dementia mortality. We begin by investigating the characteristics of dementia mortality through absolute numbers of death and the percentage share of dementia mortality to overall mortality. Subsequently, we delve into a spatial analysis of dementia mortality. This spatial analysis is further stratified based on different dementia classifications (dementia or AD) and is segregated by sex, with separate analyses for men and women. Shifting to PD, we initiate the section by characterizing PD mortality, followed by a spatial analysis that is subsequently stratified by sex.

Dementia mortality

Characteristics of dementia deaths

- 21 We employed two broad ICD categories to define mortality associated with dementias: dementia (ICD8: 290, ICD9: 290, ICD10: F00-F03), and AD (ICD9: 331, ICD10: G30). Figure 2 shows a notable shift in dementia classification between 1980 and 1993, with the code for dementia (ICD9: 290) giving way to the AD code (ICD9: 331) as the primary classification for dementia-related deaths. From 1993 onward, the absolute number of deaths associated with dementia surpassed those attributed to AD. We see a decrease of AD deaths and a peak of dementia deaths in 1998-2000, the period in which classification transitioned from ICD-9 to ICD-10. This is peculiar given that in many countries AD recorded deaths peaked during this period [Anderson & Rosenberg, 2003; Niu et al., 2017]. From 2000 until 2013 AD mortality continues to rise. From 2013-2016 AD mortality stabilizes, while dementia mortality continues to rise.

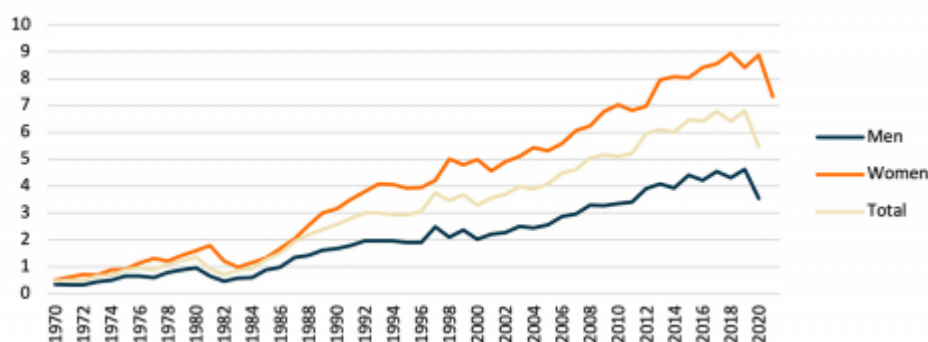
Figure 2 Dementia deaths in absolute numbers, Belgium 1970-2020



Source: Statistics Belgium

- 22 Figure 3 illustrates the percentage share of dementia deaths to total mortality, including both dementia and AD. Notably, dementia mortality has significantly increased since the 1980's, from hardly 1% to about 9% in 2019. A decline in dementia deaths is observed in the year 2020, most likely attributed to the impact of the COVID-19 crisis during that period. Additionally, dementia contributes to a higher proportion of deaths in women compared to men. This gender gap in dementia mortality widens significantly over the years. This is noteworthy, given that the gender gap in life expectancy at older ages in Belgium has narrowed since the 1990s [Eggerickx et al., 2020].

Figure 3 Percentage share of dementia deaths to total mortality by sex, Belgium 1970-2020



Source: Statistics Belgium, calculations by author

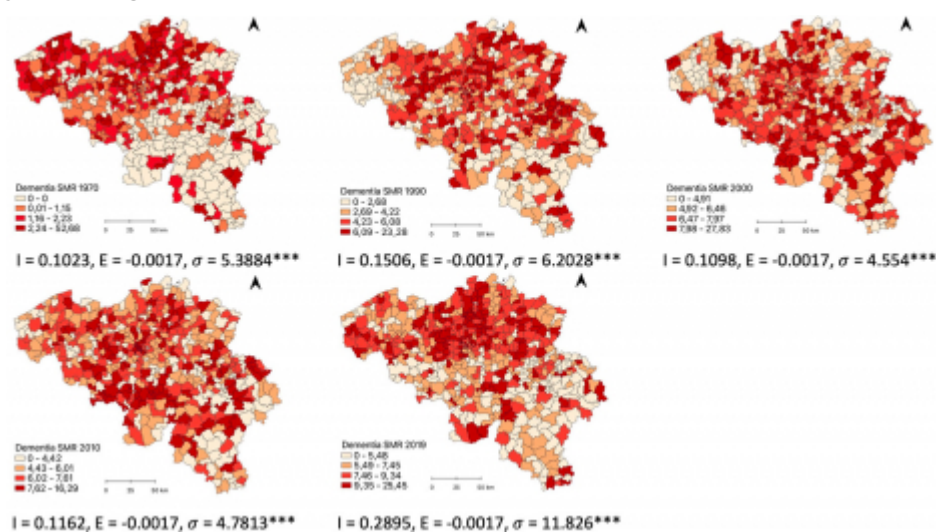
Geographical distribution of dementia mortality

- 23 The spatiotemporal evolution of total dementia mortality (combined dementia and AD codes), as illustrated in Figure 4, reveals distinctive patterns over the decades. In 1970, a concentrated prevalence of dementia-related mortality was observed in Flanders, gradually extending to the Walloon provinces of Hainaut and Liège by 1990, while experiencing a decline in West Flanders. By 2000, dementia mortality exhibited a more uniform distribution across Belgium, with the exception of persistently low

mortality rates in West Flanders. This diffuse trend persisted in 2010, with notable exceptions such as an increase in dementia mortality in West Flanders and notably low rates in the provinces of Liège and Luxembourg.

- 24 In 2019, a significant resurgence of dementia mortality was observed in Flanders, deviating from the preceding patterns. This spatial clustering is further underscored by Moran's I statistics, revealing a consistent positive autocorrelation across all five time periods. Notably, in 2019, this autocorrelation reached a substantially higher level ($I = 0.2895$, standard deviation = 11.826, $p = 2.2e-16$) compared to other time-periods, emphasizing a distinctive and statistically significant clustering of dementia mortality in Flanders during that period. Overall, dementia mortality seemed to be clustered in densely populated and urban areas. Throughout the years, mortality rates were high in the urban areas of Brussels and Antwerp.

Figure 4 Standardized total dementia mortality rates (per 10,000 population aged ≥ 45 years), Belgian municipalities 1969-1970, 1989-1991, 2000-2002, 2009-2011, and 2017-2019



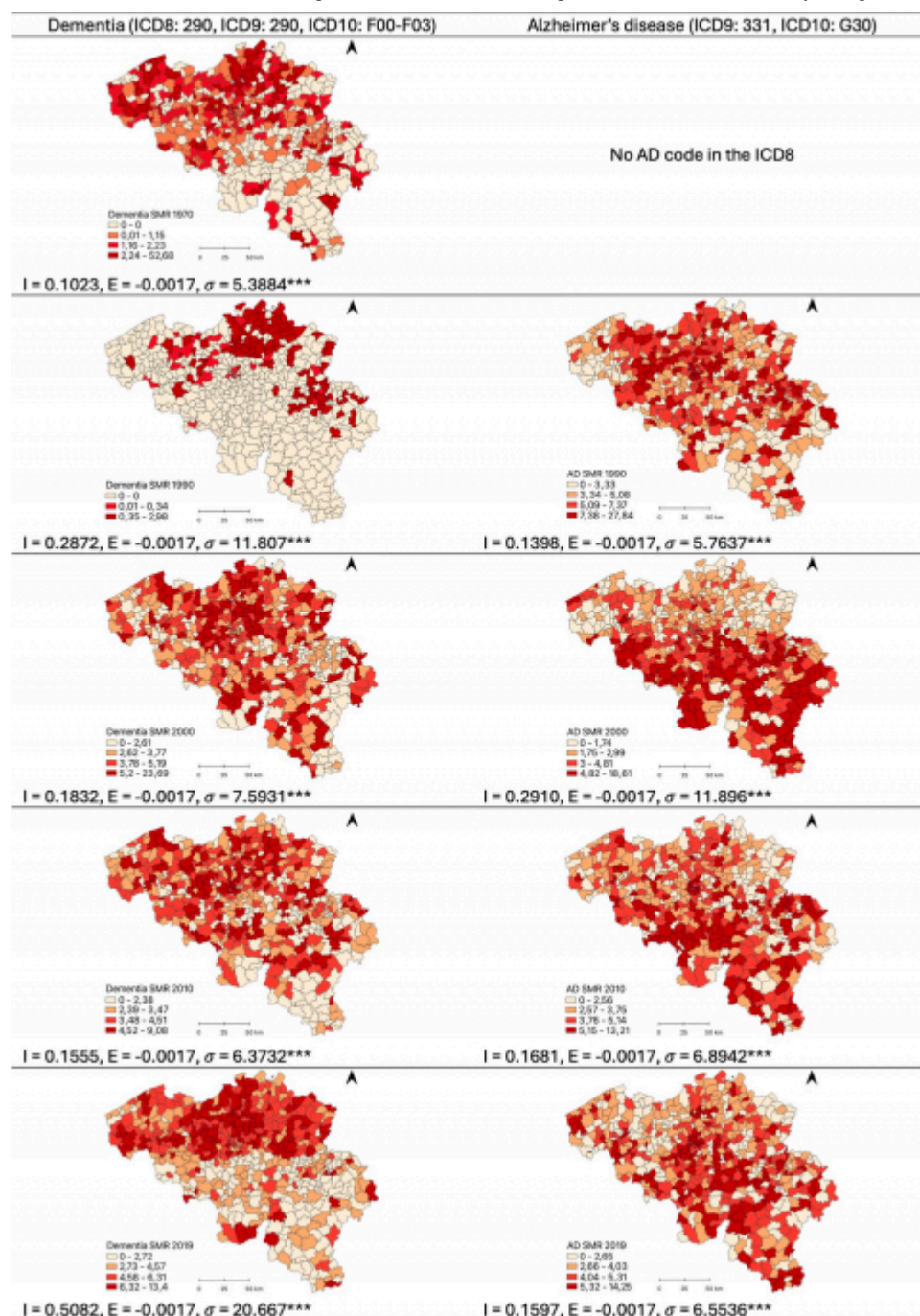
I = Moran's I statistic, E = Expected value, σ = Standard deviation, $^{***} = p < 0.001$

Source: Statistics Belgium, calculations by author

- 25 In figure 5, we examine the ICD categories dementia (ICD8: 290, ICD9: 290, ICD10: F00-F03) and AD (ICD9: 331, ICD10: G30) separately, unveiling distinct spatial dynamics in the distribution of related deaths. Prior to the introduction of an ICD code for AD, dementia-related deaths were predominantly concentrated in Flanders in 1970. The positive Moran's I value ($I = 0.1023$, standard deviation = 5.3884, $p = 3.554e-08$) underscores a positive spatial autocorrelation during this period. Following the widespread adoption of the AD classification by 1990, a noticeable shift occurred in the spatial distribution of dementia-related deaths across Belgium. The Moran I value increased to 0.1398, (standard deviation = 5.7637, $p = 4.113e-09$), indicating an intensified positive spatial autocorrelation. Interestingly, the dementia classification persists in specific regions within Flanders, particularly in Antwerp, and in some municipalities in Limburg and East Flanders, as suggested by a Moran's I value of 0.2872 (standard deviation = 11.807, $p = 2.2e-16$).

- 26 By 2000, a distinct north-south divide in classification became apparent, with the dementia classification more prevalent in Flanders, while the AD classification was more pronounced in the Walloon region. This spatial pattern persisted in 2010 and 2019. Notably, by 2019, the Moran's I value has risen to 0.5082 (standard deviation = 20.667, $p = 2.2e-16$), indicating a substantial increase in positive spatial autocorrelation, highlighting the evolving and region-specific nature of dementia and AD classifications over the years.

Figure 5 Standardized dementia and AD mortality rates (per 10,000 population aged ≥ 45 years), Belgian municipalities 1969-1970, 1989-1991, 2000-2002, 2009-2011, and 2017-2019



I = Moran's I statistic, E = Expected value, σ = Standard deviation, *** = $p < 0.001$

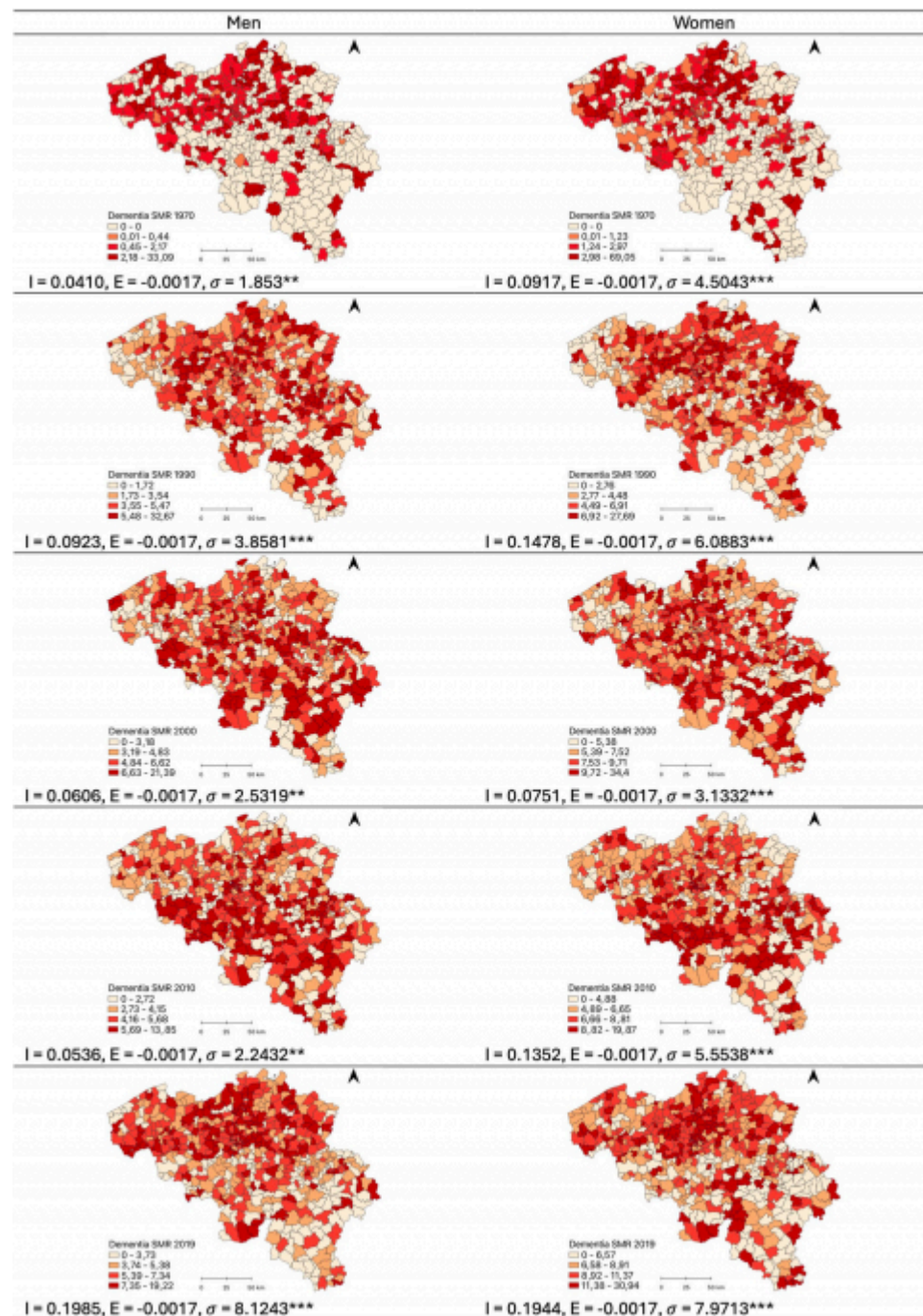
Source: Statistics Belgium, calculations by author

Spatial variations of dementia mortality by sex

- 27 In figure 6, we examine sex-based disparities in total dementia mortality. While the spatial distribution of dementia does not exhibit pronounced variations by sex, subtle distinctions emerge. In 1970, female dementia deaths seemed to be more diffused throughout Flanders, while for men, dementia is more clustered in specific municipalities. By 1990, a notable distinction surfaced in the provinces of Namur and the north of Luxembourg, where dementia mortality is evident in men but not in women, while minimal differences are observed between men and women in 2000. In 2010, male dementia mortality forms a cluster in the entire southwestern part of Belgium, spanning the provinces of Hainaut, Namur, and the northern part of Luxembourg. In contrast, for women, the clustering is more centrally located, encompassing Hainaut and Liège. By 2019, the spatial pattern has become very similar again. Moran's I statistics indicate a significant positive autocorrelation for both sexes across all five time periods. However, the values for men are closer to zero,

accompanied by standard deviations with lower levels of significance. This suggests a lower degree of spatial clustering among men when compared to women.

Figure 6 Standardized total dementia mortality rates (per 10,000 population aged ≥ 45 years) by sex, Belgian municipalities 1969-1970, 1989-1991, 2000-2002, 2009-2011, and 2017-2019



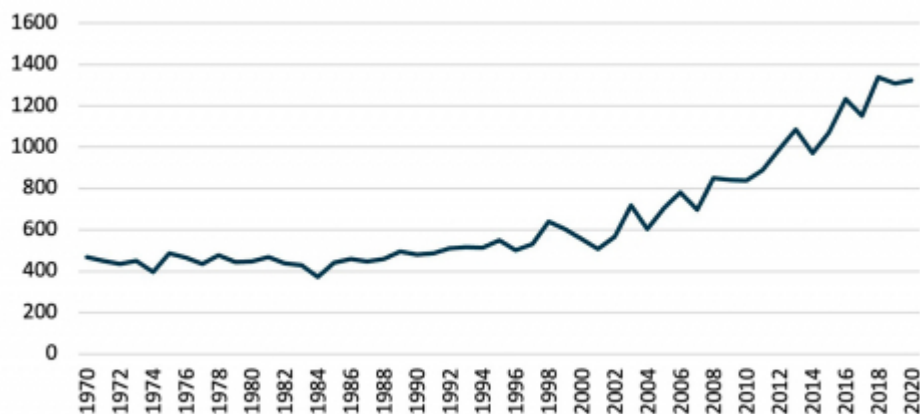
I = Moran's I statistic, E = Expected value, σ = Standard deviation, ** = $p < 0.05$, *** = $p < 0.001$

Source: Statistics Belgium, calculations by author

PD mortality

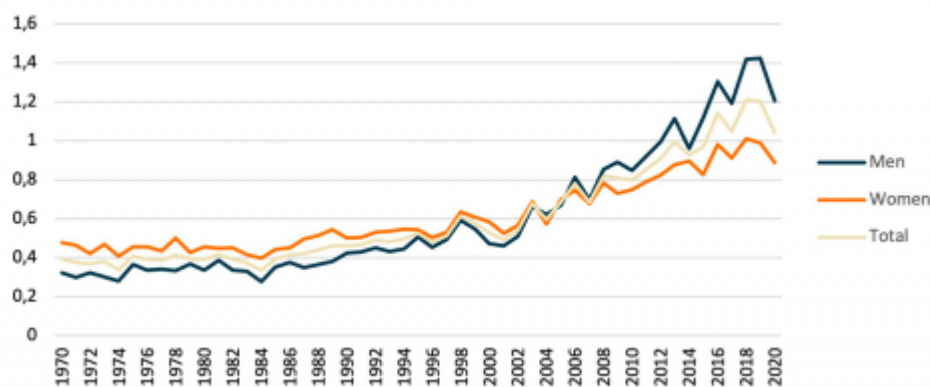
Characteristics of Parkinson's disease deaths

- 28 In figure 7, the absolute deaths from PD are illustrated. Between 1997 and 2020, PD-related deaths in Belgium more than doubled, increasing from 533 to 1,325. This trend aligns with findings from the United States, where Rong et al. [2021] reported a significant increase in PD mortality from 1999 to 2019.

Figure 7 Absolute Parkinson's disease deaths, Belgium 1970-2020

Source: Statistics Belgium

- 29 Analysing the share of PD deaths to total mortality (figure 8) reveals a noteworthy shift. Prior to 2004, PD accounted for a higher proportion of deaths among women; however, from 2004 to 2020, it emerged as a more predominant factor in the mortality rate among men. The male predominance of PD, initially described by William Gowers in the 1880s [Goetz, 2011], is well established, with men considered at greater risk, being affected twice as often as women [Baldereschi et al., 2000].

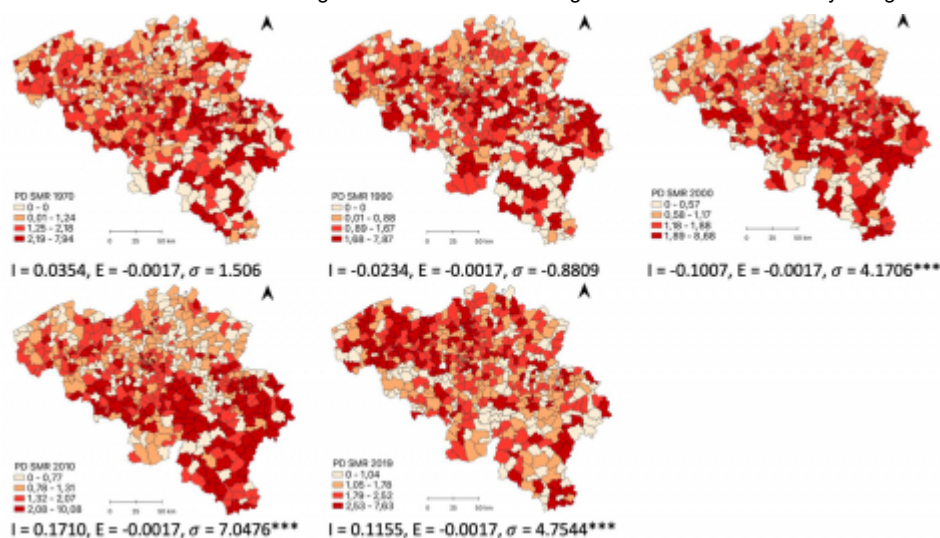
Figure 8 Percentage share of Parkinson's disease deaths to overall mortality by sex, Belgium 1970-2020

Source: Statistics Belgium

Geographical distribution of PD mortality

- 30 Upon examining PD mortality across municipalities (Figure 9), a subtle increase is observed in Flanders between 1970 and 1990. Notably, the province of Luxembourg consistently exhibits relatively lower PD mortality rates compared to other regions in the country during these periods. However, the Moran's I statistics reveal no significant spatial autocorrelation in 1970 and 1990. By the year 2000, a distinct shift in PD mortality rates is observable. There is a notable increase in PD mortality rates in the Walloon region, surpassing the mortality rates in Flanders. This pattern persists in 2010. However, by 2019, the trend has reversed, with higher PD mortality in Flanders compared to the Walloon region. The Moran's I statistics indicate significant positive autocorrelations in the periods of 2000, 2010, and 2019. Unlike dementia mortality, PD mortality does not seem to be clustered in densely populated areas.

Figure 9 Standardized mortality rates (per 10,000 population aged ≥ 45 years) Parkinson's disease, Belgian municipalities 1969-1970, 1989-1991, 2000-2002, 2009-2011, and 2017-2019



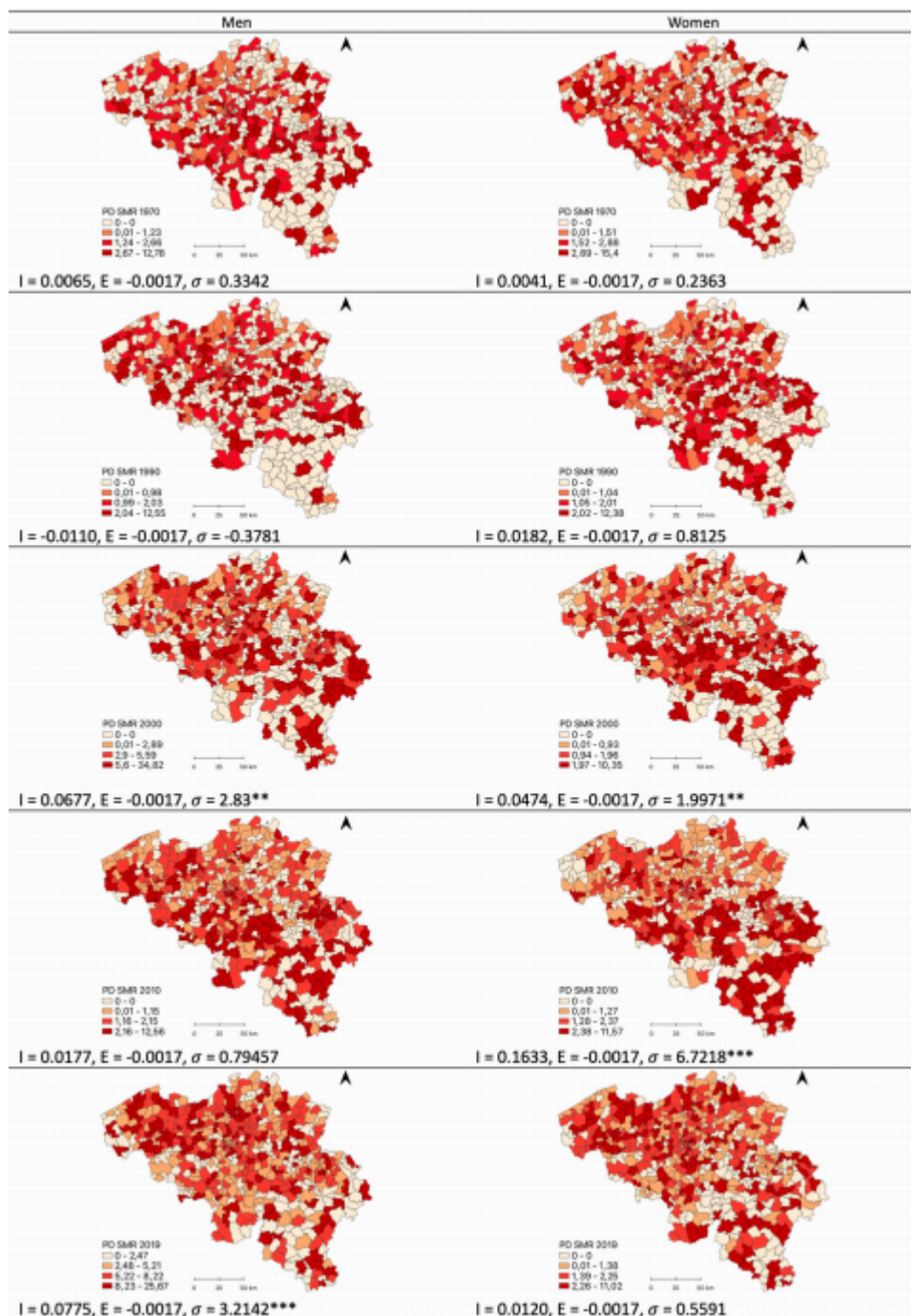
I = Moran's I statistic, E = Expected value, σ = Standard deviation, *** = $p < 0.001$

Source: Statistics Belgium, calculations by author

Spatial variations in Parkinson's disease mortality by sex

- 31 In Figure 10, the age-standardized mortality rates are presented by sex. Between the years 1970 and 1990, a notable increase in PD mortality is observed in the Flanders region. This rise is particularly pronounced among men, showing a more substantial increase compared to women during these two decades. Conversely, in 2000 and 2010, Parkinson's disease mortality appears to be higher in the Walloon region in both men and women, supported by the Moran's I statistics revealing positive spatial autocorrelation. In 2019, the trend reversed with higher PD mortality in Flanders compared to the Walloon region. However, this pattern in 2019 is statistically significant only for men ($I = 0.0775$, standard deviation = 3.2142, $p = 0.0007$).

Figure 10 Standardized mortality rates (per 10,000 population aged ≥ 45 years) Parkinson's disease by sex, Belgian municipalities 1969-1971, 1989-1991, 2000-2002, 2009-2011, and 2017-2019



I = Moran's I statistic, E = Expected value, σ = Standard deviation, ** = $p < 0.05$, *** = $p < 0.001$

Source: Statistics Belgium, calculations by author

7. Discussion

32 This comprehensive study delves into the spatiotemporal variations in NDD mortality, with a specific focus on dementias and PD in Belgium spanning from 1970 to 2020. Filling a critical gap in the existing literature, this research provides a thorough examination over five decades, revealing insightful perspectives into the evolving patterns of NDD mortality.

33 Initially, we analysed total dementia mortality, employing two broad ICD categories together (dementia: ICD8: 290, ICD9: 290, ICD10: F00-F03; and AD: ICD9: 331, ICD10: G30). Our findings indicate a significant increase in dementia related mortality since the 1980's. This increasing trend is observed across Europe, likely influenced by factors such as the increase in life expectancy, better diagnostics, and environmental factors [Niu et al., 2017]. Spatial analysis revealed significant clustering of dementia in Flanders in 1970 and 1990. By 2000, dementia mortality exhibited a more uniform

distribution across Belgium. This trend persisted in 2010. In 2019, a significant resurgence of dementia mortality was observed in Flanders, deviating from the preceding patterns. A possible explanation for these persistent higher dementia mortality rates in Flanders is the higher life expectancy in this region [Eggerickx et al., 2020]. However, considering we used age-standardization techniques, it is probable that socioeconomic- and environmental factors also play a significant role.

34 Secondly, we examined the categories of dementia and AD separately. The findings uncover a significant shift in classification between 1980 and 1993, with the code for dementia (ICD9: 290) giving way to the AD code (ICD9: 331) as the primary classification for dementia-related deaths. This transition can be attributed to advancements in scientific understanding of these diseases. When Alois Alzheimer initially described a cognitive condition characterized by neurofibrillary tangles and neuronal degeneration around 1910, it was considered a rare presenile condition [Assal, 2019; Goedert & Ghetti, 2007]. In 1970, Tomlinson, Blessed, and Roth found that most of the dementias emerging after the age of 65 exhibited the same neurofibrillary degeneration as those described by Alois Alzheimer. Consequently, AD evolved from a rare disease until the 1970s to an epidemic, garnering the majority of the diagnoses related to neurodegenerative conditions [Vatanabe et al., 2020]. From 1993 onward, absolute deaths associated with dementia surpassed those attributed to AD. From 2013 to 2016, AD mortality stabilized, while dementia mortality continued to rise.

35 These classification disparities in dementia are also spatially noticeable. In 1970, before the existence of a specific ICD-code for AD, dementia significantly clustered in Flanders. By 1990, the AD classification became widespread throughout Belgium, while the dementia classification persisted in specific regions of Flanders. In 2000, a clear distinction emerged with the dementia classification clustering in Flanders and the AD classification in the Walloon region. This distinction remained significant in 2010 and 2019. Therefore, we hypothesize that Flemish doctors tend to use the dementia classification more, while Walloon doctors prefer the AD classification on death certificates, possibly related to a difference in the medical programs at universities in the northern (Dutch speaking) part of Belgium compared to the southern (French speaking) part. Studies in the United States [Akushevich et al., 2021] and Australia [Jorm et al., 1989] have also suggested that registration practices play a significant role in spatial variations of dementia mortality.

36 Finally, there was also a distinction in dementia related deaths between the sexes. Dementia contributed to a higher proportion of deaths in women compared to men. This gender gap in dementia mortality widens significantly over the years. The female dominance is seen in dementia mortality throughout Europe [Niu et al., 2017]. Outspoken mortality trends for women have been attributed to genetic, hormonal and social factors, as well as the longer life expectancy of women [Mielke et al., 2014]. Spatially, there was no discernible difference between sexes.

37 For PD, we found that PD-related deaths in Belgium more than doubled between 1997 and 2020. This observed trend aligns with findings from the United States, where Rong et al. [2021] reported a significant increase in PD mortality from 1999 to 2019. The authors proposed various explanations for this increase, including changes in exposure factors over the past decades, such as the documented rise in traffic-related air pollution [Lee et al., 2016], known to elevate the risk of PD [Palacios, 2017]. Additionally, the notable decrease in smoking behavior [Savica et al., 2016], which has been suggested to mitigate the risk of PD [Li et al., 2015], may contribute to this increase. While the Gompertzian hypothesis (as individuals experience extended lifespans, they develop age-related diseases hardly apparent in earlier life stages) is considered, it is acknowledged that age standardization was applied, indicating that this theory may not account for all observed patterns in their study. Lastly, the enhanced accuracy of registration practices is recognized as a potential factor influencing the outcomes of death certificates [Darweesh et al., 2018; Goldacre et al., 2010]. In Belgium, we found no significant spatial autocorrelation of PD mortality in 1970 and 1990. In 2000, the Walloon region experienced a notable increase in PD mortality rates,

surpassing those of Flanders. By 2019, this pattern has changed, with higher PD mortality rates in Flanders compared to the Walloon region. Further research is needed to investigate the reasons behind this regional discrepancy.

38 When studying sex differences in PD-related deaths, we found that before 2004, PD accounted for a higher proportion of deaths among women, but from 2004 to 2020, it became a more predominant factor in the mortality rate among men. The male predominance of PD, initially described by William Gowers in the 1880s [Goetz, 2011], is well established, with men considered at greater risk, being affected twice as often as women [Baldereschi et al., 2000]. Nevertheless, contradictory trends have been observed, with several studies reporting higher mortality rates for PD in women between 1951 and 1987 [Chió et al., 1993; Diamond et al., 1990], aligning with our findings. Interestingly, the literature continues to reference these older articles (e.g. [Cerri et al., 2019]), perpetuating the assumption of a persistent female predominance in PD mortality. However, recent research challenges this notion. A study from Spain reported higher PD mortality in men from 2010 to 2019 [Gómez-Mayordomo et al., 2023], aligning with our findings of increased male PD mortality from 2004 to 2020. This underscores the importance of considering more recent and region-specific data to accurately characterize the evolving landscape of PD mortality trends. Similar to dementia, there were no significant differences in spatial clustering of PD mortality between men and women.

39 Strengths of this study include the rich extensive database, enabling a study over a five-decade timeframe. To our knowledge, this is the first study investigating NDD mortality patterns over such a considerable period of time. Moreover, the spatial mapping at municipality-level allows for a detailed investigation of mortality patterning. Lastly, we took possible sex differences into account by studying men and women separately after examining the overall mortality patterns. Despite these strengths, the study also has some limitations. First, neurodegenerative diseases tend to be underreported on death certificates [Benito-León et al., 2014; Romero et al., 2014]. This makes it plausible that the disease burden is underestimated. Furthermore, we used the underlying cause of death throughout the years to be consistent with the oldest data, this has the possibility of excluding some deaths related with NDDs compared to a multiple cause approach [Korhonen et al., 2020] which includes all death certificates with any mention of the above outcomes as an underlying, immediate, intermediate, or additional cause of death. Additionally, our study reveals the importance of registration practices on mortality data, this is especially noticeable when looking at the regional differences in classification of dementia versus AD. While Vandormael et al. [2018] suggested that the complex chain of causes of deaths used in the Flemish forms might contribute to the underreporting of dementia on death certificates, there is a lack of insights into the decision-making processes or potential regional variations in guidelines. Future research should aim to provide greater clarity on these aspects to mitigate underreporting and enhance the reliability of NDD-associated mortality data.

8. Conclusion

40 In conclusion, this study explored the spatiotemporal variations in NDD mortality, with a focus on dementias and PD in Belgium from 1970 to 2020. The study reveals significant findings regarding dementia mortality, demonstrating a substantial increase since the 1980s. Spatial analysis highlights higher dementia mortality in Flanders. The examination of dementia and AD separately uncovers a notable shift in classification between 1980 and 1993, reflecting advancements in scientific understanding. Spatial disparities in classification between Flemish and Walloon regions suggest variations in registration practices, with dementia registrations clustered in Flanders and AD registrations clustered in the Walloon regions. Gender differences in dementia-related death reveal a widening gap over the years.

- 41 For PD, the study identifies a significant increase in PD-related deaths between 1997 and 2020. Spatial analysis shows a notable rise in PD mortality rates in the Walloon region by 2000, yet a contrasting pattern was found in 2019. Sex differences in PD-related deaths exhibit a shift from higher mortality among women before 2004 to a more predominant impact on men from 2004 to 2020. Similar to dementia, PD mortality displayed no significant spatial differences between men and women.
- 42 This research underscores the intricate dynamics of NDD mortality, emphasizing the need for nuanced interpretation considering evolving disease classifications, gender differences, and regional variations. It calls for future research to address underreporting issues and adopt a more comprehensive approach to refine our understanding of NDD mortality patterns.

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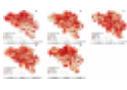
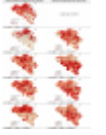



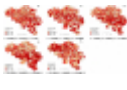

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Notes

1 Mortality- and population data from 1970 to 1991 were derived from the LOKSTAT-database, Ghent University, Quetelet Center. Mortality- and population data from 1991 to 2020 were derived from the National Mortality Database, Vrije Universiteit Brussel, Brussels Institute for Social and Population Studies (BRISPO)

Table des illustrations

	Titre	Figure 1 Belgian regions, provinces, and municipalities
	Crédits	Source: Map constructed by author
	URL	http://journals.openedition.org/eps/docannexe/image/14680/img-1.jpg
	Fichier	image/jpeg, 372k
	Titre	Table 1 Number of deaths in Belgium (1970-2020) with dementia or PD diagnoses coded according to ICD, revisions 8 (1970-1978), 9 (1979-1995), and 10 (1996-2020)
	Légende	N = number of deaths
	Crédits	Source: Statistics Belgium
	URL	http://journals.openedition.org/eps/docannexe/image/14680/img-2.jpg

	Fichier	image/jpeg, 168k
	Titre	Figure 2 Dementia deaths in absolute numbers, Belgium 1970-2020
	Crédits	Source: Statistics Belgium
	URL	http://journals.openedition.org/eps/docannexe/image/14680/img-3.jpg
	Fichier	image/jpeg, 128k
	Titre	Figure 3 Percentage share of dementia deaths to total mortality by sex, Belgium 1970-2020
	Crédits	Source: Statistics Belgium, calculations by author
	URL	http://journals.openedition.org/eps/docannexe/image/14680/img-4.jpg
	Fichier	image/jpeg, 140k
	Titre	Figure 4 Standardized total dementia mortality rates (per 10,000 population aged ≥ 45 years), Belgian municipalities 1969-1970, 1989-1991, 2000-2002, 2009-2011, and 2017-2019
	Légende	I = Moran's I statistic, E = Expected value, σ = Standard deviation, *** = $p < 0.001$
	Crédits	Source: Statistics Belgium, calculations by author
	URL	http://journals.openedition.org/eps/docannexe/image/14680/img-5.jpg
	Fichier	image/jpeg, 468k
	Titre	Figure 5 Standardized dementia and AD mortality rates (per 10,000 population aged ≥ 45 years), Belgian municipalities 1969-1970, 1989-1991, 2000-2002, 2009-2011, and 2017-2019
	Légende	I = Moran's I statistic, E = Expected value, σ = Standard deviation, *** = $p < 0.001$
	Crédits	Source: Statistics Belgium, calculations by author
	URL	http://journals.openedition.org/eps/docannexe/image/14680/img-6.jpg
	Fichier	image/jpeg, 948k
	Titre	Figure 6 Standardized total dementia mortality rates (per 10,000 population aged ≥ 45 years) by sex, Belgian municipalities 1969-1970, 1989-1991, 2000-2002, 2009-2011, and 2017-2019
	Légende	I = Moran's I statistic, E = Expected value, σ = Standard deviation, ** = $p < 0.05$, *** = $p < 0.001$
	Crédits	Source: Statistics Belgium, calculations by author
	URL	http://journals.openedition.org/eps/docannexe/image/14680/img-7.jpg
	Fichier	image/jpeg, 1,0M
	Titre	Figure 7 Absolute Parkinson's disease deaths, Belgium 1970-2020
	Crédits	Source: Statistics Belgium
	URL	http://journals.openedition.org/eps/docannexe/image/14680/img-8.jpg
	Fichier	image/jpeg, 140k
	Titre	Figure 8 Percentage share of Parkinson's disease deaths to overall mortality by sex, Belgium 1970-2020
	Crédits	Source: Statistics Belgium
	URL	http://journals.openedition.org/eps/docannexe/image/14680/img-9.jpg
	Fichier	image/jpeg, 144k
	Titre	Figure 9 Standardized mortality rates (per 10,000 population aged ≥ 45 years) Parkinson's disease, Belgian municipalities 1969-1970, 1989-1991, 2000-2002, 2009-2011, and 2017-2019
	Légende	I = Moran's I statistic, E = Expected value, σ = Standard deviation, *** = $p < 0.001$
	Crédits	Source: Statistics Belgium, calculations by author
	URL	http://journals.openedition.org/eps/docannexe/image/14680/img-10.jpg
	Fichier	image/jpeg, 504k
	Titre	Figure 10 Standardized mortality rates (per 10,000 population aged ≥ 45 years) Parkinson's disease by sex, Belgian municipalities 1969-1971, 1989-1991, 2000-2002, 2009-2011, and 2017-2019
	Légende	I = Moran's I statistic, E = Expected value, σ = Standard deviation, ** = $p < 0.05$, *** = $p < 0.001$

Crédits	Source: Statistics Belgium, calculations by author
URL	http://journals.openedition.org/eps/docannexe/image/14680/img-11.jpg
Fichier	image/jpeg, 1012k

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Référence électronique

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Auteurs

Janna Dinneweth

Brussels Institute for Social and Population Studies (BRISPO),
Vrije Universiteit Brussel, Department of Sociology,
Pleinlaan 5, 1050 Brussels (Belgium)
[janna.dinneweth\[at\]vub.be](mailto:janna.dinneweth[at]vub.be)

Sylvie Gadeyne

-  IDREF : <https://idref.fr/103143912>

VIAF

ALF

- **VIAF** : <http://viaf.org/viaf/9243491>



• **ISNI** : <https://isni.org/isni/0000000037363762>

Brussels Institute for Social and Population Studies (BRISPO),
Vrije Universiteit Brussel, Department of Sociology,
Pleinlaan 5, 1050 Brussels (Belgium)
Sylvie.Gadeyne[at]vub.be

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