Trends in Dementia Epidemiology, Multi- and Comorbidity in Flanders from 2000 to 2015: a Longitudinal Retrospective Cohort study on the Intego Database

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Prologue:

The subject of this master thesis was chosen because of the increasing proportion of elderly patients with dementia in our population. As a general practitioner we are often confronted with these elderly patients. As the composition of a population changes, its comorbidity profiles change along with it. This has a direct impact on our work as a general practitioner. I have myself experienced the difficulties when treating patients with dementia, because of a lack of applicable guidelines on when and how to treat comorbidities in this specific population. It is thus important to map the changes in dementia prevalence and its comorbidity profiles in order to create applicable guidelines for the management of elderly patients with dementia. This master thesis aims to study the changes in dementia prevalence and its comorbidity profiles in Flanders, Belgium.

I would like to express my gratitude to prof. dr. Jan De Lepeleire for reaching such an interesting topic for this master thesis and for his many contributions in literature and in expert opinion. Furthermore, I would like to thank prof. dr. Bert Vaes for his advice and assistance with the statistical analysis. Lastly, my thanks go out to prof. dr. Frans Boch Waldorff for his expert opinion and international contribution to this paper from the very beginning.

Trends in Dementia Epidemiology, Multi- and Comorbidity in Flanders from 2000 to 2015: a Longitudinal Retrospective Cohort study on the Intego Database

Abstract
Context: With the aging of our population it seems plausible that the prevalence of both dementia and multimorbidity will increase in the following decades.
Objectives: The aim of this study was firstly to examine the changes in dementia prevalence and incidence from 2000 to 2015. Second, to assess the trend in prevalence of multimorbidity and comorbidity in patients with dementia over the same 16-year time period.
Methods: Data were collected from the Intego Database, a Belgian general practice-based morbidity registration network, from 1 January 2000 to 31 December 2015. The results were processed through joinpoint regression analyses using the SEER*Stat software and through Cochran-Armitage tests and Jonckheere-Terpstra tests using the R Software V.3.3.2.
Results: Data from 1893 patients aged 65 years and older were available for assessment. From 2000 to 2015 the age-adjusted prevalence of dementia significantly increased from 1,19 % to 2,24 %. Furthermore, almost all age-adjusted and age- and gender specified prevalences nearly doubled. Incidence however, remained stable with a non-significant rising trend from 3,70 to 4,96. More than half of the patients with dementia suffered from multimorbidity and this amount significantly increased over fifteen years. By 2015, 73,00 % and 59,40 % of the patients with dementia suffered from two or more or three or more chronic conditions respectively. Hypertension, lipid metabolism disorders and osteoarthritis were the most prevalent conditions.
Conclusion: This study demonstrates a significant rise and a nearly doubling in dementia prevalence over a fifteen-year time period. Furthermore, these results confirm that many patients with dementia suffer from multimorbidity and that this number too is rising.
Keywords: dementia, epidemiology, multimorbidity, comorbidity

Abstract:
Context: Door de vergrijzing van de populatie, is het waarschijnlijk dat zowel de prevalentie van dementie als van multimorbiditeit zullen toenemen de komende decennia.
Doel: Het doel van deze studie was ten eerste om de veranderingen in prevalentie en incidentie van dementie in kaart te brengen van 2000 tot en met 2015. Ten tweede, om de trend in prevalentie van multimorbiditeit en comorbiditeit bij patiënten met dementie te bestuderen over dezelfde tijdsperiode.
Methoden: Gegevens werden verkregen van de Intego Database, een Belgisch morbiditeitsregistratienetwerk van huisartsenpraktijken, van 1 januari 2000 tot en met 31 december 2015. De resultaten werden bekomen door joinpoint regressie analyses aan de hand van de SEER*Stat software en door middel van Cochran-Armitage and Jonckheere-Terpstra tests met behulp van de R Software V.3.3.2.
Resultaten: Data van 1893 patiënten van 65 jaar en ouder waren beschikbaar voor analyse. In de periode van 2000 tot en met 2015 nam de leeftijdgecorrigeerde prevalentie van dementie significant toe van 1,19 % tot 2,24 %. Bovendien vertoonden bijna alle leeftijdgecorrigeerde en de leeftijds- en geslachtsspecifieke prevalenties zo goed als een verdubbeling. De incidentie bleef echter stabiel met een niet-significante, stijgende trend van 3,70 naar 4,96. Meer dan de helft van de patiënten met dementie leed aan multimorbiditeit en dit aandeel nam significant toe op vijftien jaar tijd. Tegen 2015 leed 73,00 % en 59,40 % van de patiënten met dementie aan respectievelijk twee of meer of drie of meer chronische aandoeningen. Hypertensie, vetstofwisselingsstoornissen en artrose waren de meest voorkomende comorbiditeiten.
Conclusie: Deze studie toont een significante toename en zo goed als een verdubbeling van de prevalentie van dementie over een periode van vijftien jaar. Bovendien bevestigen de resultaten dat veel patiënten met dementie aan multimorbiditeit lijden en dat dit aandeel van patiënten stijgt.
Sleutelwoorden: dementie, epidemiologie, multimorbiditeit, comorbiditeit

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Introduction

Dementia is an age-related clinical syndrome that comprises multiple underlying pathophysiological changes in the brain, which eventually lead to an impairment of mental functioning, activities of daily living and behavior. The World Health Organization (WHO) states that there are 10 million new diagnoses of dementia annually and that 50 million people are living with dementia worldwide currently [1]. Furthermore, the total number of people living with dementia is expected to nearly double every 20 years [1-3]. In Flanders, the estimated prevalence of dementia increases from 10 % at the age of 65 to 20 % at the age of 80 and up to 40 % at an age of 90 years and older [4-5]. The subject of dementia is more actual than ever, since the WHO has recognized dementia as a public health priority [1]. The management of health and social care for people with dementia should comprise early diagnosis, effective treatment, education and support for carers and advanced care planning. For many of these aspects, primary care practitioners are best placed to coordinate care and to deliver person-centered care [2].

Another age-related phenomenon is multimorbidity, defined as the coexistence of two or more chronic diseases in one person [6-7]. This matter too has gained interest over the last years, because growing evidence suggests that multimorbidity is associated with increased risk of mortality, poor functional status, reduced quality of life and greater use of health care services [8]. Multimorbidity provides a global functional view of the patient and implies a shift from the single disease paradigm to a more global functional view of the patient. This should also be one of the core competencies of a family practitioner [6,9-10-11]. With the aging of our population it seems plausible that the prevalence of both dementia and multimorbidity will increase in the following decades [4,9]. This is an important evolution because growing evidence suggests that additional comorbidity can accelerate the cognitive decline in patients with dementia. Adversely, dementia can complicate diagnosis and clinical care of other medical conditions and may undermine the patients' self-management [12]. Nevertheless, only limited

research has been performed on the changes in dementia prevalence and incidence and in related multi- and comorbidity. This is reflected in the lack of accurate data on dementia prevalence and in the lack of applicable guidelines on multi- and comorbidity in patients with dementia [13]. In order to fill this gap in literature, this study analyzed the trend of dementia prevalence and incidence and the trend of dementia related multi- and comorbidity from 2000 to 2015.

Methods

Data collection

In this longitudinal retrospective registry-based cohort study we investigated the epidemiology and comorbidity of the index disease dementia in Flanders, Belgium [7]. Data were obtained from the Intego database, a Belgian general practice-based morbidity registration network at the Department of General Practice at the Catholic University of Leuven [14]. In 2015 the Intego database possessed data from 440 140 different patients. This practice population was calculated to represent 1,91 % of the Flemish population by age and gender. The database contained anonymized information about new diagnoses, drug prescriptions, laboratory results and biomedical parameters. All data were obtained from the electronic health records of over 100 general practitioners working at more than 50 practices evenly spread throughout Flanders [14-15]. These data were all registered using computer-generated keywords, internally linked to codes. New diagnoses were thus classified according to a thesaurus automatically linked to the International Statistical Classification of Diseases of Primary Care (ICPC-2) and the International Statistical Classification of Diseases and related Health Problems (ICD-10) [14,16]. These classification systems were both accepted by the WHO for coding in primary practice [17]. New data were collected on a yearly basis by means of specially framed extraction software, subsequently entered in a central database and then historically accumulated for each patient. The quality of the data was guaranteed firstly by selecting only those general practices with an exquisite registration performance. This required that the number of new diagnoses per

patient per year had to be higher than one, the percentage of diagnoses encoded without using keywords was less than five percent and both of these parameters remained stable for at least three years. Second, the database was externally validated by means of national and international comparisons and internally validated using tracers as a measure of correctness [14,16]. From this database we selected all incident cases older than 65 years of age for whom between 1 January 2000 to 31 December 2015 the ICPC-2 code 'P70' for dementia was registered. The yearly contact group (YCG) was used as the denominator. Research demonstrated that in countries without decapitation the YCG approximated 80 % of the practice population [18]. Furthermore, in elderly the YCG nearly approached the entire practice population, since most elderly tended to visit their GP at least once annually [18].

Ethics

The procedures were approved by the Belgian Privacy Commission and the ethical review board of the Faculty of Medicine at the Catholic University of Leuven (no. ML1723).

Dementia

Dementia was coded 'P70' by the ICPC-2 classification. Only patients aged 65 years and older were included, because young dementia concerned only a rare subgroup. No further differentiation was made among the subtypes of dementia.

Multimorbidity and comorbidity

Multimorbidity is generally defined as the coexistence of two or more chronic diseases in one person, whereas comorbidity is defined as any disease or risk factor that may interact with one index disease [6]. Multimorbidity was analyzed as the coexistence of two or more chronic diseases and as the coexistence of three or more chronic conditions in one person, in order to identify those patients with higher care needs [9]. Dementia itself was accounted for as one chronic condition. This implied that multimorbidity was present from the moment that one or two other chronic conditions were diagnosed, depending on the operational definition mentioned above. A list of chronic conditions, as implemented by Knottnerus et al. and adapted

by Smeets et al. for similar research, was used to study multimorbidity [16,19]. This list is available in attachment. Parkinson's disease (N87) and HIV/AIDS (B90) were excluded from the index list because of possible interaction with the etiology of dementia. Psychiatric comorbidities were excluded from the list as well, because of diagnostic difficulty between psychiatric and dementia symptoms [20]. The same index list of chronic diseases was used to examine the most prevalent chronic comorbidities in patients with dementia.

Data analysis

Five-year age groups were formed starting from 65 years of age until 90 years and older. First, we calculated the prevalence (/1000 patients) and incidence (/1000 patient years at risk) of dementia by gender and by age. Next, the trend in dementia prevalence and incidence rates for every age group and gender was calculated from 2000 to 2015 using a joinpoint regression analysis. A joinpoint is a point in the trend curve where a statistically significant change in the trend over time is observed. The annual percentage change (APC) and the average annual percentage change (AAPC) can be calculated from this joinpoint regression model [16,21]. The 16-year time period was divided into four time intervals of four years (2000-2003, 2004-2007, 2008-2011 and 2012-2015). For this joinpoint regression analysis the SEER*Stat software (Joinpoint Trend Analysis software from the Surveillance Research Program of the US National Cancer Institute (http://surveillance.cancer.gov/jointpoint)) was used. Third, to calculate the prevalence of multimorbidity (/100 patients) and its time trend in incident dementia cases, the 16-year time period was again divided into four intervals of four years and the Cochran-Armitage test was used. This test for trend is used to associate a binary response to an ordinary variable with k categories [16,22]. This analysis was performed for the two operational definitions of multimorbidity, namely as the presence of two or more and as the presence of three or more chronic conditions. Finally, the trend in comorbidity profiles in incident dementia cases was explored for the most prevalent comorbidities, using the Jonckheere-Terpstra test for these same time intervals of four years. The Jonckheere-Terpstra trend test is used to associate

a continuous response with an ordinal variable with k categories [16,22]. Both analyses were performed using the R Software V.3.3.2 (Free Software Foundation, Boston, Massachusetts, USA) (Desktools and clinfun packages) [16]. For each analysis, the level of significance was set on $p < 0,05$.

Results

Study population

The total study population between January 2000 and December 2015 consisted of 1893 patients with dementia aged 65 years and older. The mean age of the study population was 81 years old. Over 60 % of the study population were women, although their share showed a statistically significant decrease during the study period. (Table 1)

Table 1: Study population characteristics.

	2000-2003	2004-2007	2008-2011	2012-2015	Trend test P value
Study population					
Patients 'P70'	n =338	n = 454	n =564	n =537	
Mean age (SD)	81,0 (6,97)	80,5 (6,93)	81,2 (6,84)	81,4 (6,62)	0,0256
Females, n (%)	235 (69,53)	302 (66,52)	363 (64,36)	332 (61,82)	0,0146

Trends in age-standardized prevalence and incidence of dementia (2000-2015)

The age-standardized prevalence of dementia showed a significant upward trend for the entire study population from 1,19 % in 2000 to 2,24 % in 2015 (AAPC 4,0; 95 % CI 3,4 to 4,6). A similar, significant upward trend was seen in males (AAPC 5,2; 95 % CI 4,4 to 6,1). The overall trend for women was significantly rising as well, but consisted of a steep increase in prevalence from 2000-2005 (AAPC 8; 95 % CI 4,3 to 11,9) and a less steep, positive trend from 2005-2015 (AAPC 2,4; 95 % CI 1,4 to 3,3). Furthermore, these rising trends showed a nearly doubling in prevalence for the total and female population and a more than doubling in prevalence for the male population. (Figure 1, Table 2)

The age-standardized rate for incidence showed a non-significant rising trend for the total and female population (AAPC 0,9; 95 % CI -0,8 to 2,6 and AAPC 0,5; 95 % CI -0,7 to 1,7

respectively). Yet in men, a significant rise in incidence was noted from 3,45 in 2000 to 4,91 in 2015 (AAPC 1,9; 95 % CI 0,1 to 3,6). (Figure 1, Table 2)

Figure 1. Age-standardized prevalence (/1000) and incidence (/1000) of dementia in the Intego Database for the entire population, females and males from 2000-2015.

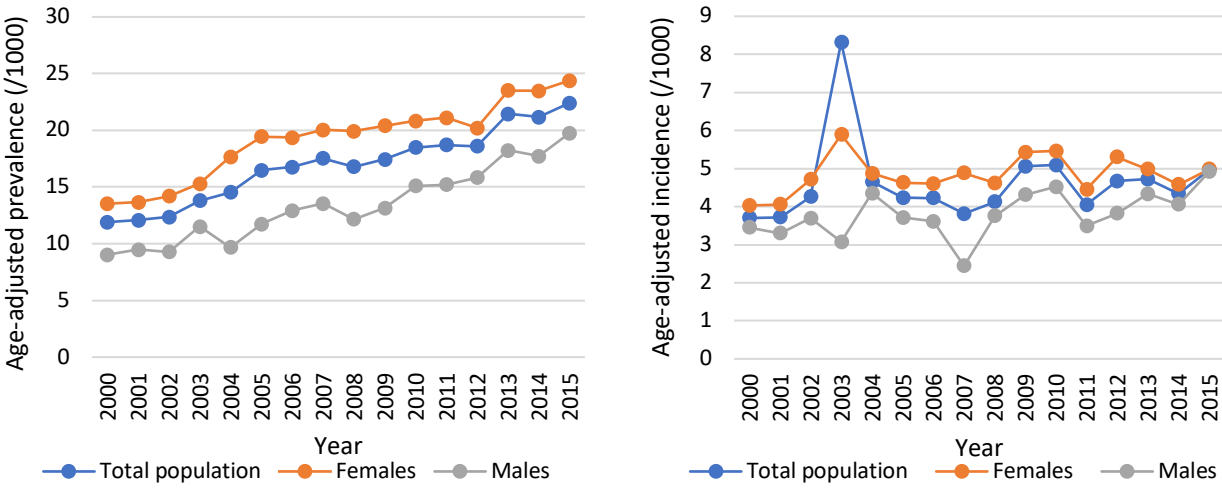


Table 2: Trends in age-adjusted prevalence (/1000) and incidence (/1000) of dementia by gender from 2000-2015. ((A)APC: (average) annual percentage change)

				Trend 1		Trend 2	
	Year 2000	**Year 2015**	**AAPC [95% CI]**	**Years**	**APC [95% CI]**	**Years**	**APC [95% CI]**
Prevalence (/1000)							
Total	11,90	22,41	4,0 [3,4;4,6]	2000-2015	4,0 [3,4;4,6]		
Female	13,53	24,90	4,2 [3,0;5,4]	2000-2005	8,0 [4,3;11,9]	2005-2015	2,4 [1,4;3,3]
Male	9,03	19,76	5,2 [4,4;6,1]	2000-2015	5,2 [4,4;6,1]		
Incidence (/1000)							
Total	3,70	4,96	0,9 [-0,8;2,6]	2000-2015	0,9 [-0,8;2,6]		
Female	4,03	4,98	0,5 [-0,7;1,7]	2000-2015	0,5 [-0,7;1,7]		
Male	3,45	4,91	1,9 [0,1;3,6]	2000-2015	1,9 [0,1;3,6]		

Trends in prevalence and incidence of dementia per age group and gender (2000-2015)

By the end of the study period in 2015 the prevalence of dementia ranged from 0,87 % at the age of 65-69 to 2,40 % at the age of 75-79 and up to 6,63 % at the age of 90+ years old. (Table 3) The prevalence per age group showed a significantly rising trend for all of the age groups from 65 to 89 years old, as demonstrated by their respective AAPC's in table 3. For the age group 75-79 years an overall significant upward trend was seen for the total population and for males. However, for females an overall non-significant rising trend was perceived, starting with a significant rise (APC 7,4; 95 % 4,8 to 10,2), followed by a very strong, non-significant decline

(APC -13,1; 95 % CI -31 to 9,4) and a less steep, non-significant increase (APC 7,5; 95 % CI -5,7 to 22,5) in prevalence. In patients aged 90 years and older increasing, though non-significant, prevalences were noted as well. (Figure 2, Table 3)

The AAPC's of the age- and gender specified incidence rates showed non-significant increases and decreases for all age-groups. (Table 4)

Figure 2: Prevalence (/1000) of dementia for females and males for every age-group from 2000-2015.

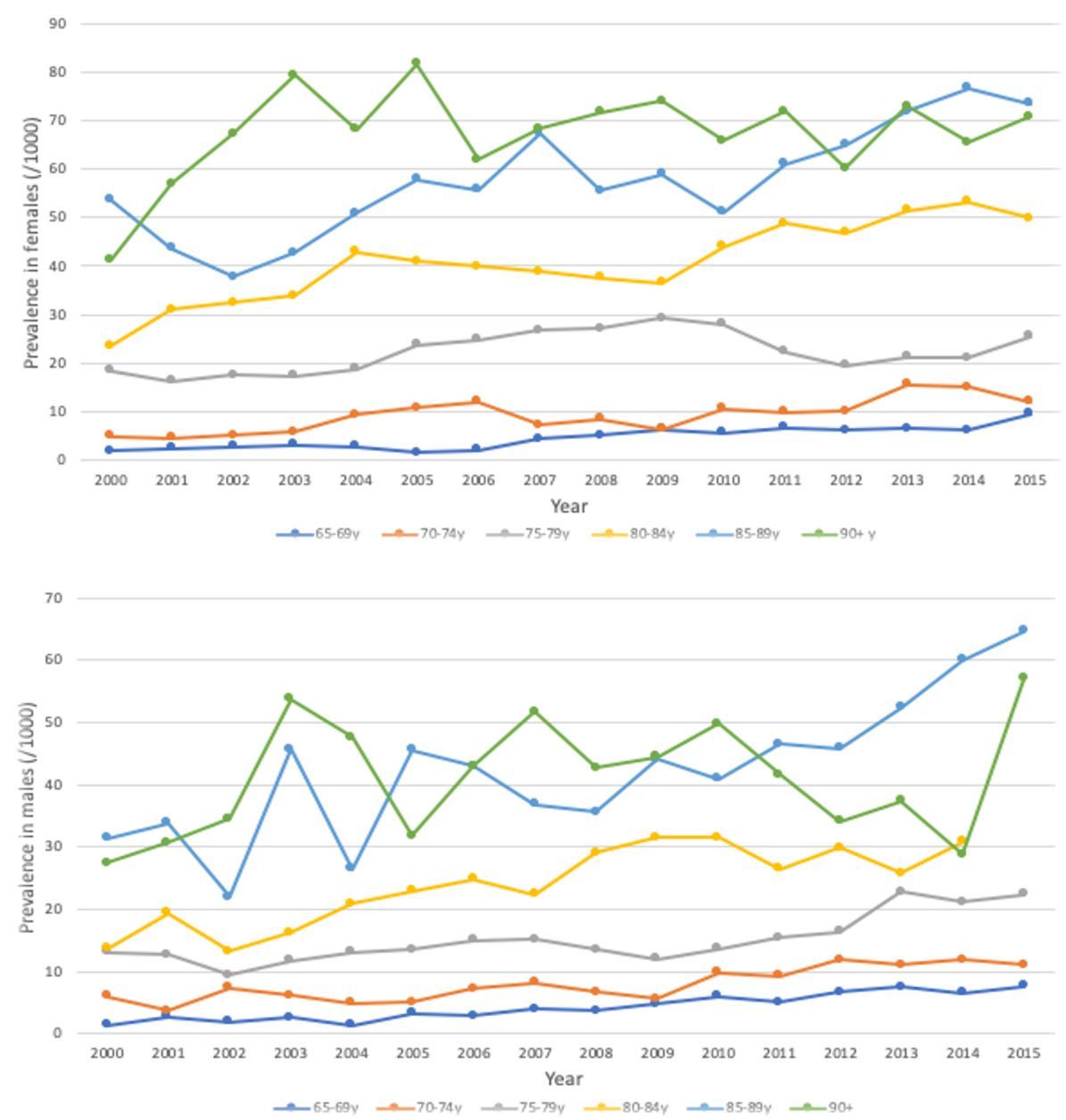


Table 3: Trends in dementia prevalence rates (/1000) for every 5-year age group and gender from 2000-2015. ((A)APC: (average) annual percentage change)

				Trend 1		Trend 2		Trend 3	
	Year 2000	**Year 2015**	**AAPC [95%CI]**	**Years**	**APC [95%CI]**	**Years**	**APC [95%CI]**	**Years**	**APC [95%CI]**
Prevalence 65-69y (/1000)									
Total	1,69	8,68	10,4 [8,3;12,6]	2000-2015	10,4 [8,3;12,6]				
Female	1,97	9,65	10,0 [7,0;13,1]	2000-2015	10,0 [7,0;13,1]				
Male	1,36	7,69	10,6 [8,2;13,1]	2000-2015	10,6 [8,2;13,1]				
Prevalence 70-74y (/1000)									
Total	5,47	11,58	6,2 [4,1;8,3]	2000-2015	6,2 [4,1;8,3]				
Female	4,99	12,11	5,9 [2,7;9,3]	2000-2015	5,9 [2,7;9,3]				
Male	6,06	11,03	6,2 [3,8;8,6]	2000-2015	6,2 [3,8;8,6]				
Prevalence 75-79y (/1000)									
Total	16,18	24,04	3,0 [0,7;5,2]	2000-2007	5,8 [1,5;10,3]	2007-2015	0,5 [-2,2;3,4]		
Female	18,44	25,49	3,0 [-1,7;7,9]	2000-2009	7,4 [4,8;10,2]	2009-2012	-13,1 [-31,0;9,4]	2012-2015	7,5 [-5,7;22,5]
Male	13,12	22,31	4,6 [1,6;7,7]	2000-2010	1,6 [-1,7;5,0]	2010-2015	11,1 [3,3;19,4]		
Prevalence 80-84y (/1000)									
Total	18,24	41,55	3,9 [2,9;5,0]	2000-2015	3,9 [2,9;5,0]				
Female	23,58	49,81	3,6 [2,4;4,9]	2000-2015	3,6 [2,4;4,9]				
Male	9,41	30,83	5,5 [2,4;8,8]	2000-2010	9,4 [5,3;13,6]	2010-2015	-1,7 [-8,3;5,3]		
Prevalence 85-89y (/1000)									
Total	46,07	70,04	3,7 [2,5;4,9]	2000-2015	3,7 [2,5;4,9]				
Female	53,59	73,36	3,4 [2,0;4,8]	2000-2015	3,4 [2,0;4,8]				
Male	31,38	64,65	4,7 [2,8;6,6]	2000-2015	4,7 [2,8;6,6]				
Prevalence 90+y (/1000)									
Total	38,17	66,33	2,5 [-1,1;6,1]	2000-2003	17,9 [-2,3;42,3]	2003-2015	-1,1 [-2,6;0,5]		
Female	41,39	70,76	3,2 [-1,9;8,5]	2000-2002	31,6 [-13,0;99,0]	2002-2015	-0,6 [-2,0;0,8]		
Male	27,47	56,97	0,4[-2,4;3,2]	2000-2015	0,4 [-2,4;3,2]				

Table 4: Trends in dementia incidence rates (/1000) for every 5-year age group and gender from 2000-2015. ((A)APC: (average) annual percentage change)

				Trend 1		Trend 2		Trend 3	
	Year 2000	Year 2015	AAPC [95%CI]	Years	APC [95%CI]	Years	APC [95%CI]	Years	APC [95%CI]
Prevalence 65-69y (/1000)									
Total	1,06	1,43	1,5 [-1,3;4,4]	2000-2015	1,5 [-1,3;4,4]				
Female	0,79	1,89	2,7 [-1,6;7,3]	2000-2015	2,7 [-1,6;7,3]				
Male	1,36	0,97	-1,7 [-5,9;2,6]	2000-2015	-1,7 [-5,9;2,6]				
Prevalence 70-74y (/1000)									
Total	1,15	1,88	0,0 [-4,0;4,2]	2000-2015	0,0 [-4,0;4,2]				
Female	1,67	1,23	-1,2 [-6,2;4,0]	2000-2015	-1,2 [-6,2;4,0]				
Male	0,51	2,57	1,5 [-3,7;6,9]	2000-2015	1,5 [-3,7;6,9]				
Prevalence 75-79y (/1000)									
Total	3,97	5,34	2,0 [-0,9;4,9]	2000-2015	2,0 [-0,9;4,9]				
Female	4,94	6,00	0,4 [-2,1;3,0]	2000-2015	0,4 [-2,1;3,0]				
Male	2,66	4,56	4,5 [-1,1;10,4]	2000-2015	4,5 [-1,1;10,4]				
Prevalence 80-84y (/1000)									
Total	6,71	11,47	1,2 [-1,0;3,6]	2000-2015	1,2 [-1,0;3,6]				
Female	9,16	8,99	0,4 [-2,1;2,9]	2000-2015	0,4 [-2,1;2,9]				
Male	2,71	14,63	2,8 [-2,2;8,1]	2000-2015	2,8 [-2,2;8,1]				
Prevalence 85-89y (/1000)									
Total	15,60	18,83	1,4 [-2,1;5,1]	2000-2015	1,4 [-2,1;5,1]				
Female	14,72	21,53	2,5 [-1,4;6,5]	2000-2015	2,5 [-1,4;6,5]				
Male	17,28	14,49	-0,8 [-4,4;2,9]	2000-2015	-0,8 [-4,4;2,9]				
Prevalence 90+y (/1000)									
Total	11,90	10,15	-0,5 [-8,6;8,4]	2000-2010	2,7 [-0,7;6,3]	2010-2013	-22,4 [-48,1;15,9]	2013-2015	23,5 [-19,3;88,9]
Female	8,64	9,02	-2,5 [-7,0;2,2]	2000-2009	4,6 [-1,7;11,2]	2009-2015	-12,3 [-20,2;-3,6]		
Male	22,60	12,50	-2,5 [-7,4;2,7]	2000-2015	-2,5 [-7,4;2,7]				

Trends in multimorbidity and comorbidity profiles (2000-2015)

This analysis revealed a high prevalence of multimorbidity. When defined as the coexistence of two or more chronic conditions, more than half of the patients with dementia suffered from multimorbidity. Furthermore, this proportion increased significantly (p = 0,0088) over the past fifteen years from 64,20 % to 73,00 %. When defined as the presence of three or more chronic conditions, the prevalence of multimorbidity was lower. Nonetheless, the prevalence remained high and demonstrated a significant increase from 48,82 % to 59,40 % (p = 0,02) during the study period as well. (Table 5)

Hypertension (41,34 %), lipid metabolism disorders (28,68 %) and osteoarthritis (18,99 %) had the highest prevalence and remained the most prevalent comorbidities throughout the

Table 5: Prevalence (/100) of multimorbidity as 2 or ≥ 3 chronic conditions and comorbidity profiles in incident dementia cases using the Cochrane-Armitage test from 2000-2015.

	2000-2003	2004-2007	2008-2011	2012-2015	Trend test P value
Multimorbidity prevalence (/100)	*n (%)*	*n (%)*	*n (%)*	*n (%)*	
2 chronic conditions	217 (64,20)	331 (72,91)	425 (75,35)	392 (73,00)	0,0088
≥3 chronic conditions	165 (48,82)	265 (58,37)	358 (63,48)	319 (59,40)	0,0200
Comorbidity prevalence (/100)	*n (%)*	*n (%)*	*n (%)*	*n (%)*	
Hypertension (K86)	96 (28,40)	165 (36,34)	241 (42,73)	222 (41,34)	<0,001
Lipid metabolism disorder (T93)	60 (17,75)	92 (20,26)	155 (27,48)	154 (28,68)	<0,001
Osteoarthritis (L91)	52 (15,38)	79 (17,40)	94 (16,67)	102 (18,99)	0,2221
Back pain, no radiation (L84)	47 (13,91)	66 (14,54)	88(15,60)	83 (15,46)	0,4706
Cerebrovascular accident (K90)	42 (12,43)	60 (13,22)	69 (12,23)	57 (10,61)	0,3028
Osteoporosis (L95)	39 (11,54)	66 (14,54)	82 (14,54)	80 (14,90)	0,2244
Knee osteoarthritis (L90)	38 (11,24)	75 (16,52)	87 (15,43)	78 (14,53)	0,3916
Ischemic heart disease (K74)	37 (10,95)	58 (12,78)	61 (10,82)	51 (9,50)	0,2650
Atrial fibrillation (K78)	36 (10,65)	76 (16,74)	74 (13,12)	90 (16,76)	0,0825
Type 2 diabetes (T90)	36 (10,65)	84 (18,50)	103 (18,26)	81 (15,08)	0,2355
Constitutional eczema (S87)	24 (7,10)	49 (10,79)	60 (10,64)	62 (11,55)	0,0647
Asthma (R96)	22 (6,51)	36 (7,93)	55 (9,75)	61 (11,36)	0,0081
Atherosclerosis (K92)	28 (8,28)	44 (9,69)	61 (10,82)	42 (7,82)	0,8132
Heart failure (K77)	20 (5,92)	42 (9,25)	44 (7,80)	37 (6,89)	0,9867
COPD (R95)	25 (7,40)	42 (9,25)	45 (7,98)	46 (8,57)	0,7856
Hip osteoarthritis (L89)	28 (8,28)	38 (8,37)	53 (9,40)	54 (10,06)	0,2889
Parkinsonism (N87)	15 (4,44)	37 (8,15)	32 (5,67)	27 (5,03)	0,6319
Urinary incontinence (U04)	19 (5,62)	34 (7,49)	48 (8,51)	50 (9,31)	0,0444
Irritable bowel syndrome (D93)	20 (5,92)	33 (7,27)	35 (6,21)	32 (5,96)	0,7633

entire study period. A significant increase in prevalence was seen for hypertension (p = <0,001), lipid metabolism disorders (p = <0,001), asthma (p = 0,0081) and urinary incontinence (p = 0,0444). Cerebrovascular accident (p = 0,3028), ischemic heart disease (p = 0,2650) and atherosclerosis (p = 0,8132) were the only comorbidities to show slight, though non-significant, decreases in prevalence by 2015. The prevalence of the other conditions remained rather stable. The most remarkable change was the replacement of cerebrovascular accident and ischemic heart disease by eczema and asthma in the top ten of the most prevalent chronic comorbidities. (Table 5)

Discussion

The most interesting findings of our analysis were the overall significantly rising trends and nearly doubling of dementia prevalences from 2000 to 2015. Regarding multimorbidity, our results revealed that more than half of the patients with dementia suffered from two or more chronic conditions. Furthermore, this burden significantly increased over the past fifteen years, as shown by the significantly rising trends in multimorbidity prevalence.

Comparison to other studies

Study population

The proportion of women in our analysis corresponded to the proportion mentioned in similar studies. Bauer et al., Clague et al. and Chen and colleagues reported a female proportion of 70,4 %, 70,6 % and 63,6 % respectively. However, during the study period the proportion of women in our analysis declined significantly. Furthermore, age-adjusted incidence showed a significantly rising trend only for men. This raised the question whether men were being affected by dementia more frequently nowadays than they had been in the past [23-25].

Trends in dementia prevalence and incidence

The prevalence of dementia in this analysis (1,19 % to 2,24 %) was lower than predicted by literature. According to the latest report of the Alzheimer Cooperative Valuation in Europe (Alcove) from 2013, the estimated prevalence rate of dementia in the whole of Europe was 7,23

% [26]. The Belgian Qualidem project stated that prevalence numbers for dementia in Belgium varied from 6,3 % to 9,3 % [27]. Both organizations thus reported a higher prevalence than perceived in our results. This difference could be explained by the study design and data collection method. Real life data were used in which dementia diagnosis was based on routine clinical recording instead of on assessment through a set out protocol. This may have led to an underestimation of dementia, because of difficulties with early dementia diagnosis [24]. The lower prevalences in our analysis were in line with the results of other studies with similar study designs. In a longitudinal retrospective cohort study on data of the Clinical Practice Research Datalink in the UK, Donegan and colleagues reported a rising prevalence of dementia of 0,41 % in 2005 to 0,82 % in 2015 [28]. Also, a cross-sectional analysis performed by Clague et al. on data from 314 general practices, provided by the Primary Care Clinical Informatics Unit in the UK, demonstrated a dementia prevalence of 3,6 % [24].

Apart from the oldest old, the prevalence of dementia clearly increased from 2000 to 2015. The trend analyses for dementia prevalence showed significantly upward trends for nearly all age groups until 89 years old. Besides a clear increase in prevalence, a nearly doubling of the total age-adjusted prevalence from 1,19 % to 2,24 % was noted during the study period. For the age and gender-specified prevalences too, a doubling or nearly doubling was observed. These findings corresponded to the prediction of the WHO in 2012 that the number of people living with dementia would double over twenty years' time [1]. Reasons for this increasing prevalence remained unclear and yet to be investigated. Possible explanations were long survival of patients with dementia, increased awareness for dementia diagnosis and more structured recording of patients' data in electronic medical files [28].

The incidence of dementia showed a sudden increase in 2003. A possible explanation could be the simultaneous running of the Qualidem project, which may have increased dementia awareness and diagnosis at the time. Apart from a significantly rising trend in the overall age-

adjusted incidence in males, all of the other trends for incidence were non-significant. Therefore, we concluded that the incidence of dementia remained more or less stable over the past 15 years. This could be explained in part, by an accurate management of cardiovascular risk factors through the use of statins, antithrombotic and antihypertensive agents.

It was difficult to draw any conclusions on patients aged 90 years and older, since these data showed many outliers and all of the perceived trends in these older age groups were non-significant. One explanation for the lower incidence of dementia in this group of elderly could be the relatively larger number of subjects with more favorable cardiovascular risk profiles.

Trends in multimorbidity and comorbidity profiles

The data on multimorbidity prevalence showed significantly rising trends from 2000 to 2015, whether defined as the presence of two or more or three or more chronic conditions. More than half of the patients with dementia suffered from three or more comorbidities and therefore from an even greater care need than those with only two chronic conditions [9]. These results corresponded to the findings of a similar study performed by Doraiswamy et al., who reported a prevalence of three of more comorbidities in Alzheimer's disease patients of 61,00 % [29].

The findings on the most common comorbidities in patients with dementia were in line with our expectations and with the results in similar studies. (Appendix, Table 6). Bauer et al. and Clague et al. also reported hypertension, lipid metabolism disorder, type 2 diabetes, ischemic heart disease, atherosclerosis, heart failure, cerebrovascular accident and osteoarthritis amongst the most prevalent comorbidities [23-24]. Hypertension, lipid metabolism disorder and atherosclerosis, however, are very common in subjects without dementia as well and do not necessarily bring about a large increase in care needs. In contrast, other frequent chronic conditions such as cerebrovascular accident, ischemic heart disease, heart failure and diabetes do increase care needs. Also, the significant rise in prevalence of urinary incontinence is noteworthy, because this is known to be a risk factor for permanent stay in a residential setting [23].

Strengths and weaknesses

The strengths of this study included the use of data from an existing primary care database instead of in hospital data [9,23], the use of two operational definitions of multimorbidity [9], the exclusion of acute conditions to avoid unnecessarily inflation of multimorbidity prevalence [30] and a minimization of the risk of lost to follow up by calculating multimorbidity in incident dementia cases. Lastly, our study population provided a representative sample of the entire Flemish population.

A limitation of this study was the fact that diagnoses were based on physician documentation and could not be validated via clinical examinations, neither for dementia, nor for comorbidity. Also, the database did not provide any information on whether dementia diagnosis was made by a general practitioner or through a diagnostic evaluation in a memory clinic. Therefore, the validity of the individual diagnosis could be questioned and we could not fully exclude that some comorbid conditions had been misdiagnosed. Furthermore, because of the lack of detailed information on different dementia etiologies, we could not generalize the results of this analysis to specific dementia subtypes. Also, no statements could be made on psychiatric comorbidities because these were excluded from the list of chronic conditions. Another limitation was the lack of information on the severity of comorbidities, which made it impossible to assign a weight to different chronic conditions and to classify them for their respective care needs [10]. Lastly, no causality could be ascertained and comparisons to the healthy population could not be made because of the study design.

Conclusion

This study demonstrated that the incidence of dementia remained stable for women and was slightly rising for men over the past 15 years. However, the prevalence of dementia increased significantly in all age groups and even doubled for the entire population. More than half of the patients with dementia appeared to be suffering from multimorbidity by means of one or two additional chronic health conditions and this proportion showed a rising trend as well. Further research on how to implement the management of comorbidity and patient-centered care in the care for patients with dementia is needed in order to set up applicable guidelines for this specific population of elderly.

Appendix

Table 6: Comparison of the prevalence (/100) of different comorbidities in patients with dementia as reported in similar studies.

Prevalence of comorbidity					
Comorbidity	**Results (2012-2015)**	**Bauer et al. (2014)**	**Clague et al. (2017)**	**Ting-Bin Chen et al. (2017)**	**Maslow et al. (2004)**
Hypertension	41,3%	73,4%	43,2%	52,9%	52,0%
Lipid metabolism disorder	28,7%	41,5%	-	16,8%	13,0%
Osteoarthritis	19,0%	11,3%	13,6%	-	20%
Back pain without radiation	15,5%	49,0%	-	-	-
Cerebrovascular accident	10,6%	32,4%	19,4%	-	-
Osteoporosis	14,9%	23,8%	-	-	19,4%
Ischemic heart disease	9,5%	39,8%	22,8%	18,5%	29%
Type 2 diabetes	15,1%	45,2%	13,3%	30,7%	23%
Asthma	11,4%	-	3,5%	4,6%	-
Atherosclerosis	7,8%	43,2%	5,2%	-	19%
Heart failure	6,9%	46,3%	6,9%	-	28%
COPD	8,6	-	9,3%	0,9%	17%
Urinary incontinence	9,3%	50,3%	-	-	-
Eczema	11,6%	-	1,2%	-	-

References

1. Greenblat C. Dementia. World Health Organisation 2019. Available at: www.who.int/news-room/fact-sheets/detail/dementia. Accessed September 21, 2019.
2. Martin P, Anders W, Maelenn G, Gemma-Claire A, Yu-Tzu W, Matthew P. World Alzheimer Report 2015. London: Alzheimer Disease International; 2015. p.82.
3. Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: A systematic review and metaanalysis. Alzheimers Dement. 2013; 9(1): 63-75.e2.
4. Steyaert J. Dementie: van begrijpen naar begeleiden. Brussel: Politeia; 2016.
5. Expertisecentrum Dementie Vlaanderen vzw. Prevalentie. Expertisecentrum Dementie Vlaanderen. Available at: www.dementie.be/home/sample-page/prevalentie/. Accessed September 21, 2019.
6. Le Reste JY, Nabbe P, Rivet C, Lygidakis C, Doerr C, Czachowski S, et al. The European General Practice Research Network Presents the Translations of Its Comprehensive Definition of Multimorbidity in Family Medicine in Ten European Languages. PLoS One. 2015; 10(1):e0115796.
7. Willadsen TG, Bebe A, Koster-Rasmussen R, Jarbol DE, Guassora AD, Waldorff FB, et al. The role of diseases, risk factors and symptoms in the definition of multimorbidity – a systematic review. Scand J Prim Health Care. 2016; 34(2): 112-21.
8. Gijsen R, Hoeymans N, Schellevis FG, Ruwaard D, Satariano WA, van Den Bos GAM. Causes and consequences of comorbidity: a review. J Clinical Epidemiol. 2001; 54(7): 661-74.
9. Fortin M, Stewart M, Poitras ME, Almirall J, Maddocks H. A Systematic Review of Prevalence Studies on Multimorbidity: Toward a More Uniform Methodology. Ann Fam Med. 2012; 10(2): 142-51.
10. Diederichs C, Berger K, Bartels DB. The Measurement of Multiple Chronic Diseases - A Systematic Review on Existing Multimorbidity Indices. J Gerontol A Biol Sci Med Sci. 2011; 66A(3): 301-11.
11. Barnett K, Mercer S, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. Lancet. 2012; 380(9836): 37-43.
12. Bunn F, Burn A, Goodman C, Rait G, Norton S, Robinson L, et al. Comorbidity and dementia: a scoping review of the literature. BMC Med. 2014; 12: 192.

13. Damiani G, Silvestrini G, Trozzi L, Maci D, Iodice L, Ricciardi W. Quality of dementia clinical guidelines and relevance to the care of older people with comorbidity: Evidence from the literature. Clin Interv Aging. 2014; 9(5): 1399-407.
14. Truyers C, Goderis G, Dewitte H, Akker Mv, Buntinx F. The Intego database: background, methods and basic results of a Flemish general practice-based continuous morbidity registration project. BMC Med Inform Decis Mak. 2014; 14(1): 48.
15. Intego. Methodiek 2017. Available at: https://intego.be/nl/Methodiek. Accessed 21 September 2019.
16. Smeets M, Vaes B, Mamouris P, Van den Akker M, Van Pottelbergh G, Goderis G, et al. Burden of heart failure in Flemish general practices: a registry-based study in the Intego database. BMJ Open. 2019; 9(1): e022972.
17. Madden R, Sykes C, Ustun TB. World Health Organization Family of International Classifications: definition, scope and purpose 2007. Available at www.who.int/classifications/en/FamilyDocument2007.pdf. Accessed at May 23, 2020
18. Bartholomeeusen S, Kim C-Y, Mertens R, Faes C, Buntinx F. The denominator in general practice, a new approach from the Intego database. Fam Pract. 2005; 22(4): 442-7.
19. van den Akker M, Buntinx F, Roos S, Knottnerus JA. Problems in determining occurrence rates of multimorbidity. J Clin Epidemiol. 2001; 54(7): 675-9.
20. Helsen A, Jacobs V, Laes N, Vervloessem H. Dementia in general practice: literature review and Intego study protocol □dissertation]. Leuven: Catholic University of Leuven; 2018.
21. Kim HJ, Fay MP, Feuer EJ, Midthune DN. Permutation tests for joinpoint regression with applications to cancer rates. Stat Med. 2000; 19(3): 335-51.
22. Alan A. Categorical data analysis. Hoboken, New Jersey: Wiley & Sons; 2002. p.734.
23. Bauer K, Schwarzkopf L, Graessel E, Holle R. A claims data-based comparison of comorbidity in individuals with and without dementia. BMC Geriatr. 2014; 14: 10.
24. Clague F, Mercer SW, McLean G, Reynish E, Guthrie B. Comorbidity and polypharmacy in people with dementia: insights from a large, population-based cross-sectional analysis of primary care data. Age Ageing. 2016; 46(1): 33-9.
25. Chen T-B, Yiao S-Y, Sun Y, Lee H-J, Yang S-C, Chiu M-J, et al. Comorbidity and dementia: A nationwide survey in Taiwan. PLoS One. 2017; 12(4): e0175475.
26. Alzheimer Cooperative Valuation in Europe. The European Joint Action on Dementia: synthesis report 2013. Available at: https://www.alcove-

project.eu/images/pdf/ALCOVE_SYNTHESIS_REPORT_VF.pdf. Accessed April 26, 2020

27. Buntinx F, De Lepeleire J. Studie dementie RIZIV UB/1240 Qualidem I eindrapport 1999-2002. Leuven-Liège; 2002. Contract No.: Chapter 3.
28. Donegan K, Fox N, Black N, Livingston G, Banerjee S, Burns A. Trends in diagnosis and treatment for people with dementia in the UK from 2005 to 2015: a longitudinal retrospective cohort study. Lancet Public Health. 2017; 2(3): e149-56.
29. Doraiswamy PM, Leon J, Cummings JL, Marin D, Neumann PJ. Prevalence and impact of medical comorbidity in Alzheimer's disease. J Gerontol A Biol Sci Med Sci. 2002; 57(3): M173-77.
30. Xu X, Mishra GD, Jones M. Evidence on multimorbidity from definition to intervention: An overview of systematic reviews. Ageing Res Rev. 2017; 37: 53-68.