

Diagnosis of Dementia in the Specialist Setting: A Comparison Between the Swedish Dementia Registry (SveDem) and the Registry of Dementias of Girona (ReDeGi)

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Abstract. The aim of this study was to compare the frequency of dementia diagnoses from two dementia registries in Europe. Patients registered between 2007 and 2013 in the Swedish Dementia Registry (SveDem; Sweden) and in the Registry of Dementias of Girona (ReDeGi; North-East of Spain) were selected. We compared sociodemographic data, Mini-Mental State Examination (MMSE) scores, dementia subtype, and medication consumption of 22,384 cases from SveDem and 5,032 cases from ReDeGi. The average age (78.1 years SveDem versus 79.7 years ReDeGi) and the gender (female 58.2% SveDem versus 61.5% ReDeGi) did not greatly differ. MMSE score at diagnosis was higher for SveDem cases (22.1 versus 17.8). Alzheimer's disease (AD) accounted for the main dementia subtype (36.6% SveDem versus 55.6% ReDeGi). The proportion of vascular dementia (VaD) and mixed dementia was higher in SveDem (18.8% versus 6.4% and 24.9 versus 13.4%), with an odds ratio (OR) and 95% confidence interval (CI) for SveDem relative to the ReDeGi of 3.41 (3.03–3.84) for VaD, and 2.15 (1.97–2.35) for mixed dementia. This was at the expense of a lower frequency of AD in SveDem (OR 0.41; 95% CI 0.39–0.44). Other dementia diagnoses such as frontotemporal dementia or dementia with Lewy bodies did not significantly differ between registries (2.3% versus 2.9%; 1.9 versus 3.1%). Large differences in medication consumption at the time of dementia diagnosis were detected (4.7 treatments SveDem versus 6.8 ReDeGi). Northern and southern European dementia cohorts differ in demographic characteristics, MMSE score at diagnosis, and drug treatment profile.

Keywords: Alzheimer's disease, dementia, epidemiology, registries

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INTRODUCTION

Disease registries are a cost-effective way of following patients and obtaining information about a disease process, and are particularly suitable in situations where experimental research is not feasible [1]. Randomized controlled trials require a sturdy working hypothesis and are subject to more ethical concerns: for these reasons a registry may be in a unique position to generate hypotheses to be subsequently confirmed in an experimental trial [1]. Additionally, registries provide information on routine clinical practice, costs, and demographic composition of patient cohorts, all vital to public health planning [2–7].

Demography, prevalence, and survival estimates in dementia vary between regions [8, 9]. This may be due to underlying differences in lifestyle and geographic factors, differences in health care systems and patient help-seeking behavior, or methodological differences in diagnostic process [9]. Understanding the origin of these differences can provide clues on disease risk factors and set objectives for public health policy. Sweden and Spain belong to the same WHO zone for geography and infant mortality (EURO A) and were grouped for prevalence estimates of dementia in the Delphi consensus, with a prevalence ranging from 1.5 to 24.8% (depending on age group) for subjects over 65 [8].

Alzheimer's disease (AD) is the most prevalent dementia subtype worldwide [8, 10], but the relative impact of different subtypes of dementia presents large regional incidence differences, even within Europe [11–14]. In a multi-center study with eight European countries, including Spain and Sweden, the incidence and prevalence of different dementia diagnoses, particularly of vascular dementia, differed greatly between countries [11, 12]. However, another study did not find differences in the odds of dementia between a composite of Spanish studies and the Kungsholmen study, in Sweden [14]. Prevalence variations are apparent even within countries, for example, in Spain, age- and sex-adjusted prevalence for dementias for +70 populations ranged between 3% and 12% depending on the geographical area [13, 15]. The age- and sex-adjusted prevalence of dementia in Kungsholmen (central Stockholm) was 17.9% at age 70 in a study from the early 2000 [16]. In Gothenburg, the prevalence of dementia in 70- to 75-year-olds ranged from 1.7 and 6.4% depending on age group, age cohort, and gender [17]. Since cardiovascular risk factors increase the risk both of AD

and vascular dementia (VaD), the local incidence of cardiovascular disease might underlie some of these differences [18, 19].

The Swedish Dementia Registry (SveDem) was created in 2007 with the aim of improving quality of care for dementia patients throughout Sweden. Between 2007 and 2013, SveDem registered 35,819 patients with coverage of around 95% of all specialist memory clinics which diagnose dementia in Sweden [20]. The Registry of Dementia of Girona (ReDeGi) was launched in 2007 and registers demographic and clinical data of all new dementia cases diagnosed at the specialist care level in a delimited geographical area in Catalonia, in the North-East of Spain [5]. Between 2007 and 2013 the ReDeGi registered 5,032 cases.

The aims of this study were to compare the frequency of dementia subtype distribution between two different dementia registries, SveDem and the ReDeGi, and to compare demographics, clinical characteristics, and medication use at time of diagnosis. Comparisons were based in the specialist outpatient diagnoses for both registries.

METHODS

Design, geographical area of reference, and study population

We used a cross-sectional design that was based on the data from all cases registered by SveDem and ReDeGi during the years 2007–2013. SveDem's objective is to eventually capture all incident dementia cases in Sweden [2, 20, 21]. Based on incidence estimates, SveDem had coverage of around 31% of all new dementia diagnoses made nationwide for 2013 (Supplementary Figure 1). However, the coverage of incident dementia diagnoses established at memory clinics is more than 90% [22]. SveDem operates within the highly decentralized Swedish healthcare system, covering an area of 449,964 km², a population of over 9.5 million and widely ranging population density with an average of 23.7 inhabitants/km [2, 20]. In the Swedish system, both primary care physicians and specialists make diagnoses of dementia, and SveDem registers both. Diagnoses of dementia with early onset and the more rare dementias such as frontotemporal dementia (FTD) and dementia with Lewy bodies (DLB) are usually performed by specialists. The ReDeGi registers all incident cases of dementia diagnosed in the outpatient specialists settings

belonging to the Health Region of Girona (HRG). Primary care physicians are encouraged to refer suspected dementia cases to specialized care, thus all diagnosis are made in specialist clinics. Diagnoses of dementia may be made in the neurology or geriatrics outpatient consultation offices or in the outpatient memory clinics located in seven public hospitals in the HRG. Based on incidence estimates, the ReDeGi currently has coverage of around 75% of all new dementia diagnoses made in the HRG [5, 6]. The HRG is located in the northeast region of Catalonia (northeast region of Spain), has an area of 5,517 km², a population of 746,410 inhabitants, and a population density of 135.3 inhabitants/km².

Registry procedure

In SveDem, newly diagnosed patients meeting ICD-10 criteria for dementia are included in the web-based registry, which provides a framework for recording aspects of diagnostic workup, treatment, care and follow-up [20, 23–25]. The national guidelines for dementia workup established by the Swedish National Board of Health and Welfare [26] are followed in over 85% of diagnoses, with testing expanded if necessary. Quality control of the database is performed by random cross-checks of histories and entries [20, 25]. Changing diagnoses within the first year is less than 5%. SveDem is collated with the national population registry to record deaths [23, 25]. At the time of work-up, patients and caregivers are informed orally and in writing about SveDem, can decline participation and withdraw consent at any time. Data is anonymized and analyzed off-site. This study was approved by the Regional ethics committee in Stockholm.

ReDeGi uses standardized criteria for case definition, and follows the guidelines proposed by the Center for Disease Control and Prevention for a surveillance system [27]. The methodological principles and the functional structure of the ReDeGi have been previously described [5]. All diagnoses are based on an interview with the patient and the caregiver, a general medical examination, hematology and blood chemistry tests, and neuroimaging diagnosis if required. A specialist technician of the ReDeGi periodically reviews the medical chart of the cases of dementia notified in each of the seven hospitals of the HRG, and registers demographic and clinical information. The collected information meets the confidentiality requirements for personal data protection in compliance with Spanish legislation.

Variables and data harmonization

In SveDem, dementia diagnoses are coded as AD, VaD, AD and VaD (mixed dementia), DLB (McKeith criteria [28]), Parkinson's-disease dementia (PDD, Movement Disorder Society Task Force criteria [29]), FTD (Manchester/Neary criteria [30]), unspecified dementia (where specific dementia diagnosis is not ascertained), and other dementia subtypes (grouping miscellaneous dementia disorders such as corticobasal degeneration or alcohol-related dementias) [25]. Simultaneously, age, gender and baseline Mini-Mental State Examination (MMSE) [31] are entered, as are residency status (living alone versus cohabiting) and place of residence (home versus institution). The number of drugs that the patient takes regularly at the beginning of diagnostic workup is used as a proxy for comorbidity [2, 32]. The presence or absence of cardiovascular medication, antipsychotics, antidepressants, anxiolytics and hypnotics is recorded. Cholinesterase inhibitors (AChEI) and N-Methyl-D-aspartate (NMDA) antagonists prescribed upon diagnosis are entered [25, 30].

In ReDeGi, dementia diagnoses are coded using the DSM-IV-TR diagnostic criteria and additional diagnostic criteria for certain subtypes of dementia (DLB [28], PDD [29], and FTD [30]). Complementary information such as sociodemographic data (age, sex, place of residence, work position, schooling level, marital status, type of housing, healthcare referral device) and clinical data (score and date of administration of the MMSE, the Blessed Dementia Rating Scale score [33] the Clinical Dementia Rating score [34], past family history of dementia, present diagnosis of hypertension, diabetes mellitus, or dyslipidemia, and past history of depressive disorder) is registered. Data of patient's medications are obtained each year by linking the ReDeGi with the database of the Public Catalan Healthcare Service (PCHS), which includes all the drugs prescribed by the PCHS physicians and that have been dispensed in pharmacy offices.

Age, gender, MMSE score, and family history of dementia in first degree relatives were variables directly comparable between registries. In order to harmonize the data, we recorded the following variables: the dementia diagnoses of the ReDeGi were reclassified according to the SveDem classification system; because the categories of the variable residency status did not match between registries, we only used the variable place of residence (home versus institution); since the ReDeGi lacks information

on the duration of the pharmacological treatments we defined the medications taken regularly by the patients as those drugs with 4 units or more dispensed during one year.

Data analysis

A descriptive analysis of the variables was performed using central tendency measures and dispersion for quantitative variables. Absolute and relative frequencies were calculated for qualitative variables. Since all cases in ReDeGi are registered in specialist memory clinics, comparisons with SveDem were restricted to specialist diagnoses. The clinical and demographic characteristics of SveDem and the ReDeGi cases were compared using Chi-square tests for categorical variables and Student *t* tests for continuous variables. In order to quantify the strength of the differences in the distribution of sex, dementia subtype, family history of dementia, and pharmacological treatment between the SveDem and the ReDeGi cases, we calculated odds ratios. We calculated Cohen's *d* to assess the effect size of the differences in continuous variables such as age and MMSE score between SveDem and the ReDeGi cases. Results are expressed as absolute numbers and percentages, means, standard deviation (SD), and 95% confidence interval (95% CI), as appropriate. Statistical test were considered to be significant with a 2-tailed *p* value < 0.05. Data processing and analysis was performed using the Stata S.E. 12.0 for Windows.

RESULTS

SveDem and the ReDeGi registered 22,384 and 5,032 incident cases of dementia at the outpatient specialist level respectively during the 7-year period. Regarding age and sex, there were no large differences between patients registered in specialist units in SveDem and patients registered in the ReDeGi. Both groups of patients had a mean age around 79 years, and gender distribution was also similar, with a majority of women in both registries, and a 1.5:1 ratio of women-to-men. The percentage of patients reporting family history of dementia in first-degree relatives was higher for SveDem cases (41.6% versus 26.6%). The place of residence differed between the registries; a higher frequency of patients from SveDem compared to patients in the ReDeGi lived in an institution (8.8% versus 4.1%) at the moment of dementia diagnosis. The MMSE mean score between the two registries showed important differences (21.1 points

[SD = 5.1] for SveDem and 17.8 points [SD = 5.4] for the ReDeGi), with a mean difference of 3.2 points (95% CI = 3.0–3.3) and a medium effect size (Cohen's *d* = 0.66 [95% CI = 0.63–0.69]). SveDem registered a higher percentage of cases in the upper range level of MMSE score, and patients in the lower range for the MMSE scoring were more frequent in the ReDeGi (Table 1).

The distribution of the different dementia diagnoses showed important differences between the two registries. Specifically, SveDem registered a lower percentage of AD cases (36.3% versus 55.6%), and a higher number of VaD (18.8 versus 6.4%) and mixed dementia (24.9 versus 13.4%) cases than the ReDeGi. Early-onset AD (EOAD) was registered more frequently in SveDem (3.3% versus 1.3%). The ReDeGi included a higher percentage of patients with other dementia diagnoses (7.2% versus 2.3%) and a lower percentage of patients with unspecified dementia diagnose (6.7% versus 10.4%) than SveDem. Table 2 shows the frequency of dementia diagnosis types for each registry. Supplementary Table 1 reports the dementia diagnoses categories stratified by age groups. When comparing the mean age for the different dementia diagnoses between the two registries it was apparent that, for each diagnostic category, the ReDeGi cases were older than the cases in SveDem. Particularly, these differences showed medium to large effect sizes for AD, DLB, FTD, and PDD (Table 3). Gender distribution across dementia subtypes was similar in both registries, except for the DLB and PDD categories, where men were more frequent in SveDem cases (Table 3). SveDem patients had significantly higher MMSE scores in all types of dementia, and these differences with the ReDeGi showed large effect sizes, irrespective of diagnosis. Excepting EOAD, the frequency of family history of dementia in first-degree relatives was higher in SveDem cases (Table 4).

In SveDem, the mean number of drug treatments at the time of diagnosis was 4.7 (SD = 3.3), while it was 6.8 (SD = 4.1) for the ReDeGi (Cohen's *d* = 0.61; 95% CI = 0.57–0.64). Regarding the medication subtypes, except for antidepressants, there were important differences between SveDem and the ReDeGi. Overall, the patients registered by SveDem consumed fewer drugs than patients in ReDeGi. The differences ranged from 5.2% less antipsychotic use to 10.1% less anxiolytics and sleeping aid use in SveDem compared to the ReDeGi (Table 5). Regarding AChEI, there was more use in SveDem for AD and mixed dementia, and more use in ReDeGi for other dementia subtypes.

Table 1
Sociodemographic characteristics of the patients included from 2007 to 2013 in specialist units in SveDem and ReDeGi

	SveDem [†] (n = 22,384)	ReDeGi* (n = 5,032)	Effect size (95% CI)
Age, mean (SD)	78.10 (8.3)	79.72 (7.5)	0.19 (0.16–0.22) ^a
Sex (female), n (%)	13,025 (58.2)	3,095 (61.5)	0.87 (0.81–0.92) ^b
Family history dementia, n (%)	6,858 (41.6)	1,309 (26.6)	1.97 (1.83–2.11) ^b
Place of residence, n (%)			
Home	20,398 (91.1)	4,654 (95.9)	2.27 (1.95–2.63)
Institution	1,961 (8.8)	197 (4.1)	
MMSE, n (%)			
24–30	8,097 (36.2)	713 (15.2)	3.51(3.22–3.82) ^b
16–23	10,175 (45.5)	2,504 (52.0)	0.83 (0.78–0.89) ^b
0–15	3,029 (13.5)	1,579 (32.8)	0.33 (0.31–0.36) ^b

MMSE, Mini-Mental State Examination; [†]SveDem: 5,914 missing values for family history of dementia; 25 missing values for place of residence; 1,083 missing values for MMSE score; *ReDeGi: 111 missing values for family history of dementia; 181 missing values for place of residence; 236 missing values for MMSE score; ^aCohen's *d*; ^bOdds ratio of SveDem cohort relative to the ReDeGi.

Table 2
Dementia diagnoses from 2007 to 2013 in SveDem and ReDeGi [n (%)]

	SveDem (n = 22,384)	ReDeGi (n = 5,032)	Odds ratio (95% CI)
Alzheimer's disease EO	740 (3.3)	68 (1.4)	2.49 (1.94–3.20)
Alzheimer's disease LO	7,396 (33.0)	2,728 (54.2)	0.41 (0.39–0.44)
Vascular dementia	4,207 (18.8)	319 (6.4)	3.41 (3.03–3.84)
Mixed dementia	5,568 (24.9)	670 (13.4)	2.15 (1.97–2.35)
Dementia with Lewy bodies	695 (3.1)	243 (4.8)	0.63 (0.54–0.73)
Frontotemporal dementia	515 (2.3)	147 (2.9)	0.78 (0.64–0.94)
Parkinson's disease dementia	426 (1.9)	158 (3.1)	0.59 (0.49–0.72)
Unspecified	2,330 (10.4)	336 (6.7)	1.62 (1.44–1.82)
Others	507 (2.3)	363 (7.2)	0.29 (0.25–0.34)

EO, early-onset; LO, late-onset. Odds ratios and 95% confidence intervals (CI) for SveDem patients, relative to ReDeGi, to fall within one of the diagnostic categories.

Table 3
Comparison of age and sex for the different dementia diagnoses in SveDem and ReDeGi

	Age (years, [mean (SD)])			Sex (female, [n (%)])		
	SveDem (n = 22,384)	ReDeGi (n = 5,032)	Cohen's <i>d</i> (95% CI)	SveDem (n = 22,384)	ReDeGi (n = 5,032)	Odds ratio (95% CI)
Alzheimer's disease early-onset	59.4 (4.3)	60.5 (3.3)	0.26 (0.23–0.29)	455 (61.5)	48 (70.6)	0.67 (0.39–1.14)
Alzheimer's disease late-onset	78.4 (6.6)	81.1 (5.6)	0.42 (0.39–0.45)	4,839 (65.4)	1,840 (67.5)	0.91 (0.83–1.00)
Vascular dementia	79.4 (7.6)	77.5 (9.1)	0.23 (0.20–0.27)	2,082 (49.5)	141 (44.2)	1.24 (0.98–1.55)
Mixed dementia	80.9 (6.7)	81.2 (5.9)	0.04 (0.01–0.07)	3,297 (59.2)	388 (57.9)	1.06 (0.89–1.24)
Dementia with Lewy bodies	76.6 (7.0)	80.6 (6.1)	0.58 (0.55–0.61)	267 (38.4)	137 (56.4)	0.48 (0.36–0.65)
Frontotemporal dementia	69.4 (9.3)	74.7 (9.4)	0.58 (0.53–0.60)	278 (54.0)	75 (51.0)	1.12 (0.78–1.62)
Parkinson's disease dementia	74.7 (6.9)	79.2 (6.2)	0.68 (0.64–0.71)	156 (36.6)	72 (45.6)	0.69 (0.47–0.99)
Unspecified	78.5 (8.9)	81.2 (7.4)	0.31 (0.28–0.34)	1,414 (60.7)	220 (65.5)	0.81 (0.64–1.03)
Others	71.7 (10.0)	74.3 (11.7)	0.23 (0.20–0.26)	237 (46.7)	173 (47.7)	0.96 (0.73–1.26)

Supplementary Tables 2–9 report the medication at time of diagnosis stratified by dementia subtype.

DISCUSSION

This study compares the frequency of dementia diagnoses in the specialist setting and patient characteristics between two dementia registries

located in the north and south of Europe. Overall, the results show clear differences regarding the frequency subtypes of the dementia diagnoses, cognitive profile, and the medication consumption profile.

All previous epidemiological studies have shown increased prevalence of dementia as age increases, from 1% in those aged 60–64 years to 70% of those aged 90 years and older [11]. The mean age of the

Table 4
Comparisons of MMSE score and family history of dementia according to dementia group between SveDem and ReDeGi

	MMSE score [mean (SD)]			Family history of dementia ([n (%)])		
	SveDem [†] (n = 21,301)	ReDeGi* (n = 4,796)	Cohen's <i>d</i> (95% CI)	SveDem [†] (n = 16,460)	ReDeGi* (n = 4,921)	Odds ratio (95% CI)
Alzheimer's disease early-onset	22.2 (4.9)	19.8 (4.8)	0.49 (0.46–0.52)	294 (48.0)	31 (46.3)	1.07 (0.64–1.78)
Alzheimer's disease late-onset	21.5 (5.1)	17.7 (5.3)	0.73 (0.70–0.77)	2730 (47.9)	807 (30.2)	2.12 (1.92–2.34)
Vascular dementia	21.2 (4.9)	18.6 (5.6)	0.51 (0.48–0.54)	972 (32.7)	52 (16.8)	2.40 (1.77–3.27)
Mixed dementia	20.9 (5.0)	17.1 (4.9)	0.76 (0.73–0.79)	1738 (41.9)	153 (23.1)	2.39 (1.98–2.90)
Dementia with Lewy bodies	21.4 (4.9)	17.2 (5.5)	0.83 (0.80–0.86)	194 (38.0)	68 (28.7)	1.51 (1.08–2.11)
Frontotemporal dementia	23.6 (5.1)	20.3 (6.1)	0.62 (0.58–0.65)	147 (36.9)	34 (23.6)	1.91 (1.23–2.95)
Parkinson's disease dementia	21.1 (4.9)	18.5 (5.0)	0.50 (0.47–0.53)	94 (32.4)	26 (16.9)	2.36 (1.44–3.84)
Unspecified	20.1 (5.5)	17.2 (5.6)	0.52 (0.52–0.55)	597 (39.0)	72 (22.4)	2.21 (1.67–2.93)
Others	21.4 (5.4)	18.1 (5.8)	0.60 (0.57–0.63)	92 (30.3)	66 (18.8)	1.88 (1.30–2.70)

[†]SveDem: 1,083 missing values for MMSE score; 5,914 missing values for family history of dementia; *ReDeGi: 236 missing values for MMSE score; 111 missing values for family history of dementia.

Table 5
Medication (ATC codification) at time of diagnosis [n (%)]

	SveDem [†] (n = 22,384)	ReDeGi* (n = 4,252)	Odds ratio (95% CI)
Anticholinesterase (N06DA) in AD and mixed dementia	10,625 (48.2)	2,340 (55.0)	0.76 (0.71–0.81)
NMDA antagonists (N06DX) in AD and mixed dementia	8,984 (66.2%)	1,821 (60.9%)	1.25 (1.16–1.36)
Antidepressants (N06AB)	2,534 (11.5)	751 (17.7)	0.60 (0.55–0.66)
Antipsychotics (N05A)	1,890 (14.0%)	611 (20.4%)	0.63 (0.57–0.70)
Anxiolytics and/or sleeping aids (N05B + N05D)	5,241 (25.1)	1,025 (24.1)	1.05 (0.97–1.13)
Cardiovascular (B01AA + B01AC + C02 + C03 + C07 + C08 + C09 + C10)	1,398 (6.2)	485 (11.4)	0.51 (0.46–0.57)
	4,456 (21.4)	1,340 (31.5)	0.58 (0.54–0.63)
	14,437 (64.5.0)	3,355 (78.9)	0.59 (0.54–0.64)

[†]SveDem: 336 missing cholinesterase inhibitors; 404 missing NMDA; 1,498 missing antidepressants; 1,503 missing antipsychotics; 1,514 missing anxiolytics or sleeping aids; 1,462 missing cardiovascular; *ReDeGi: 780 missing medication profile.

cases in both registries was just under 80 years, with a standard deviation around 8 years, indicating that the great majority of cases in both regions are diagnosed between the age range of 72 and 88 years. According to Eurostat, life expectancy at 65 years for individuals in Sweden and Spain is 20.1 and 21.4 years, respectively, thus, half of the dementia diagnoses are performed in individuals five years before their life expectancy limit, irrespective of the country. This result is in concordance with the findings from the Danish Dementia Registry which includes the secondary health system in the Capital Region of Denmark and which covers 30% of the Danish population, where the mean age at the time of diagnosis is 78.6 years [35]. Similarly, the French National Alzheimer Database, which covers nationwide secondary care, reports a mean age of 81.9 years for AD cases and 79.3 years for patients with related disorders [36]. Overall, the SveDem and ReDeGi cohorts did not greatly differ in age at diagnosis or gender. However, when stratified by dementia diagnosis, age

at onset and gender we detected differences. AD cases in SveDem were slightly younger than those from ReDeGi, while for VaD the pattern was reversed, with ReDeGi cases being younger. DLB and PDD patients in SveDem were younger and more likely to be male than their ReDeGi counterparts. SveDem patients with FTD also tended to be younger with a mean age of 70 years, while the mean for the ReDeGi patients with FTD was around 75 years.

The place of residence at the time of diagnosis is an important variable because it helps estimate the social burden for families living with the patient or the societal economic burden related to the institutionalization [37]. Although more than 90% of the patients from both registries were living in their own home or with their families, 4.7% more of Swedish patients were living in an institution at the moment of diagnostic. The French National Alzheimer Database reports 10% of patients living in nursing homes when they contact the French memory clinics for a suspicion of dementia diagnosis [36].

We detect a large difference between registries in the percentage of patients remembering a family history of dementia. Early-onset AD presented differences in frequency between registries, and had the highest frequency of family history of dementia. This result is plausible taking into account that early-onset AD has been identified as a disease strongly linked with genetic mutations in the amyloid precursor protein gene, in the presenilin 1 gene, and in the presenilin 2 gene [38]. With regard to the rest of dementia categories, the differences may result from variability in the underlying genetic profile of the populations, but also due to a recall bias of the informant or an observer bias of the medical staff during the diagnostic process.

The MMSE score at diagnosis was significantly lower in the ReDeGi cohort, with more patients scoring in the range between 0 to 15 points. These regional differences in cognitive profile have previously been described for AD [9], and it is interesting to see them replicated for other dementia subtypes (Table 4). Baseline differences in educational attainment may explain these findings [9], especially if we consider the high proportion of cases with low education in the ReDeGi [39]. The Danish registry presents a mean MMSE mean of 20.9 points for all-cause dementia and the French National Alzheimer Database a mean of 16.4 for AD patients, 18.5 for related disorders, and 25.6 for patients with mild cognitive impairment [35, 36].

Few previous studies compare dementia cohort composition between different countries in Europe, and those that do most often limit diagnosis to AD and VaD [10, 31]. The largest of these included cohorts from eight European countries, among them Sweden and Spain, and found a similar proportion of VaD (15–20%) in all studies, while the prevalence of AD varied more between studies and depended on the percentage of those diagnosed as “other dementias” [11]. In agreement with existing reports, in our study AD was the most frequently diagnosed dementia in both cohorts, but the proportion of patients receiving a diagnosis of VaD was three times higher in SveDem than in the ReDeGi (18.8% versus 6.4%) as was the mixed dementia diagnoses and these differences were made up by a proportional reduction in AD. This result matches the known North-South gradient in cardiovascular disease [40], which could justify the greater proportion of VaD in Sweden. Indeed, the incidence for cerebrovascular disease is highest in the north of Europe, decreases to its lowest in the center of Europe (including north of Spain) [40]

and then increases again as it reaches the southern coasts. Thus, Catalonia displays one of the lowest incidences of cerebrovascular disease within Europe [41]. Another Spanish study conducted in Valladolid (west of Girona but around the same latitude) found a frequency of VaD of 5.9%, comparable to the 6.4% found in the ReDeGi [42]. Interestingly, in a meta-analysis including 48 studies [43], geographical variations of VaD and AD were also described in China, where an increased prevalence of VaD was detected in the North, whereas AD prevalence was found to be similar in the North and in the South. The recent comparison between SveDem and the Danish Dementia Registry also showed a higher frequency of VaD diagnoses in Sweden (18.8% versus 15.3%), but due to the similarities between countries, differences were attributed to different tradition for interpretation of diagnostic criteria, better access to brain magnetic resonance imaging (MRI) in Sweden or referral bias, rather than a true difference in disease incidence [35]. A similar pattern was observed for the mixed dementia category, where the proportion was double in SveDem than in the ReDeGi (25% versus 13%). Traditionally the term mixed dementia is used to describe a combination of AD and VaD, and in clinical settings this diagnostic category is used to classify patients with cognitive dysfunction and impaired functioning in daily life resulting from the coexistence of AD and cerebrovascular pathology, documented either by clinical diagnostic criteria or by neuroimaging findings. Thus, according to the known North-South gradient in cardiovascular disease, it also is plausible to expect a higher number of mixed dementia diagnoses in SveDem than in the ReDeGi. However, differences between countries in the type of specialist that performed the diagnostic (neurologist, geriatrician, psychiatrist), and in the dementia workup, particularly in the high proportion of MRI performed in Sweden, may also be responsible of these findings. Indeed, a higher rate of mixed diagnosis at the expense of AD was also observed in the comparison of SveDem and the Danish Dementia Registry [35].

Other dementia subtypes are also of interest. DLB in particular is suspected to be underdiagnosed worldwide, with widely ranging estimates from 0 to 23% of all dementia diagnoses [44, 45]. In SveDem and the ReDeGi, the relative frequencies of DLB diagnosis were not significantly different, and the percentages of 3.1 and 4.8, respectively, are in line with a percentage of around 4.2 for previous community based studies [44]. PDD's diagnostic frequency

ranged between 1.9% in SveDem and 3.1% in the ReDeGi, and did not differ significantly between registries. These values are close to the 3.6% of PDD in the general population based on a previous systematic review that included 24 population-based studies to determine the prevalence of this dementia [46]. FTD is believed to occur mainly among individuals under 65 years, and prevalence studies in populations below 65 years have reported low rates (<1%) [47, 48]. The FTD's diagnostic frequency ranged between 2.3% in SveDem and 2.9% in the ReDeGi. This result is in concordance with a recent study in a population-based sample of 70–95 year old individuals that reported an overall prevalence between 1.4 and 1.9, depending on the diagnostic criteria used [49]. No significant differences were found between SveDem and the ReDeGi regarding the frequencies of unspecified dementia and other dementias diagnostic categories. The combination of these diagnoses represented 12.7% and 13.9% for SveDem and the ReDeGi, respectively.

Concerning the patients' medication profiles at the time of diagnosis, we found an increased consumption of antipsychotics by patients in the ReDeGi compared to those in SveDem. The lower MMSE score at the time of diagnosis may be related to the greater treatment with antipsychotics; however, high rates of antipsychotic consumption have been previously reported both in the ReDeGi [39, 50] and in Catalonia [51], which warrants further study regarding mortality risks, medication side-effects, and drug-drug interactions. On the other hand, cardiovascular medications were also more common in the ReDeGi than in SveDem, which seems to be in disagreement with the North-South gradient of cardiovascular risk, but may be related with the differences seen on AD/VaD rates.

Some limitations should be considered when interpreting the results hereby presented. First, we lack information on the severity of the behavioral and psychological symptoms of dementia, which would help explaining the differences seen in drug prescription. Second, we do not have information regarding the education level of the registered cases, which may help explaining the differences seen in MMSE scores. Third, although we only considered the cases diagnosed at a specialist level, we cannot rule out a selection bias due to differences in the mechanisms that lead a patient to receive a diagnosis in the two countries. Fourth, we lack information on the length of the treatments and on the dosages prescribed, as well as on over the counter medications.

Fifth, the use of different codification systems for dementia definition (ICD-10 and DSM-IV-TR) may contribute to a classification bias. However, although a discrepancy between results of diagnosing dementia depending on the diagnostic criteria used has been described, the results of a study that compared the concordance of diagnosing dementia using ICD-10 and DSM-IV in daily clinical practice in a large sample of 206 consecutively patients showed a 100% agreement [52]. Finally, there are systemic differences between care health care settings, and these could influence the time and manner of dementia diagnosis and patient populations. For example, the higher rate of cerebrospinal fluid and MRI in Swedish cohorts could lead to more mixed dementia diagnoses, since vascular lesions are easier to see in MRI and since an AD component can be detected using cerebrospinal fluid in patients with a more vascular cognitive profile. Furthermore, the greater reach of the Swedish welfare system may lead patients and clinicians to seek early diagnosis in order to receive social support. However, the purpose of this study is to compare naturalistic cohorts, diagnosed following the routine clinical practice in each setting: our cohorts are thus representative of the daily reality of clinical practice in our respective settings. Absent a simultaneous door-to-door survey with homogenized protocols and diagnostic criteria, we will never be able to compare the biological distribution of dementia diagnoses in the North and South of Europe. However, a comparison of real life cohorts represents valuable information to clinicians and policy makers seeking to translate research findings and regulations from different parts of Europe. A key strength of this study is that, regardless the geographical coverage of each registry, both have a valid and reliable method for registering the dementia diagnoses performed in the health system of their countries, allowing comparing profiles and identifying differences of dementia diagnoses between two regions in the northern and southern of Europe. Future collaborations would be of interest to compare pharmacological prescription patterns depending on dementia subtype, the course of the diseases, and mortality rates between registries.

In conclusion, our findings show differences between the profile of patients diagnosed with dementia in a Northern and a Southern European registry. There is a higher percentage of patients with AD in ReDeGi while VaD and mixed dementia are more frequent in SveDem. Although overall the age at the time of diagnosis is similar, there are differences when comparing dementia diagnoses,

with ReDeGi cases being older, specifically those with DLB, PDD, and FTD diagnoses. At the time of diagnosis, the mean MMSE score also shows clear differences between countries, with an average difference of 3.2 points higher for SveDem patients. Family history of dementia was 15% higher in patients from SveDem. The use of anti-dementia and antidepressant treatments at the time of diagnosis does not present large variations between the two registries, however, the use of antipsychotics and anxiolytics or sleeping aids is more frequent in ReDeGi dementia patients. Future longitudinal studies merging these two registries may help to assess how these clinical and demographic features affect the clinical course of the main dementia subtypes.

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SUPPLEMENTARY MATERIAL

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