Diabetes in a Large Dementia Cohort: Clinical Characteristics and Treatment From the Swedish Dementia Registry

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OBJECTIVE

We aimed to investigate the differences in clinical characteristics and pharmacological treatment associated with the presence of diabetes in a large cohort of patients with dementia.

RESEARCH DESIGN AND METHODS

A cross-sectional registry-based study was conducted using data from the Swedish Dementia Registry (SveDem). Data on dementia diagnosis, dementia type, and demographic determinants were extracted from SveDem. Data from the Swedish Patient Register and Prescribed Drug Register were combined for the diagnosis of diabetes. Data on antidiabetic, dementia, cardiovascular, and psychotropic medications were extracted from the Swedish Prescribed Drug Register. Logistic regression was used to determine whether the variables were associated with diabetes after adjustment for confounders. In total, 29,630 patients were included in the study, and 4,881 (16.5%) of them received a diagnosis of diabetes.

RESULTS

In the fully adjusted model, diabetes was associated with lower age at dementia diagnosis (odds ratio [OR] 0.97 [99% CI 0.97–0.98]), male sex (1.41 [1.27–1.55]), vascular dementia (1.17 [1.01–1.36]), and mixed dementia (1.21 [1.06–1.39]). Dementia with Lewy bodies (0.64 [0.44–0.94]), Parkinson disease dementia (0.46 [0.28–0.75]), and treatment with antidepressants (0.85 [0.77–0.95]) were less common among patients with diabetes. Patients with diabetes who had Alzheimer disease obtained significantly less treatment with cholinesterase inhibitors (0.78 [0.63–0.95]) and memantine (0.68 [0.54–0.85]).

CONCLUSIONS

Patients with diabetes were younger at dementia diagnosis and obtained less dementia medication for Alzheimer disease, suggesting less optimal dementia treatment. Future research should evaluate survival and differences in metabolic profile in patients with diabetes and different dementia disorders.

In the last decade, the amount of research focusing on the relationship between diabetes and dementia has increased substantially. Currently, both dementia and diabetes have become global health challenges. Two of the main factors contributing to this problem include aging of the population (1) and the increasing number of overweight and obese people (2).

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As of 2015, diabetes was affecting >415 million people, with an expected increase to 640 million by 2040 (3). Diabetes is a systemic disease, and the research shows that the changes in insulin signaling and glycemic regulation negatively affect brain function as well (4).

Dementia is a syndrome characterized by progressive cognitive deficit in multiple domains, behavioral and psychological symptoms (BPSD) (5), and ultimately dependency on caregivers. Alzheimer disease (AD) and vascular dementia (VaD), the most common dementia disorders, account for 60% and 20% of dementia cases, respectively (6). Patients who express both AD and cerebrovascular pathology may receive a diagnosis of mixed dementia (7). Dementia with Lewy bodies (DLB) is considered to be the third most common dementia, but the conclusive evidence is still lacking (8). Less frequent dementia disorders include Parkinson disease dementia (PDD) and frontotemporal dementia (FTD).

No disease-modifying drugs are currently available for dementia. A consensus by the British Association for Psychopharmacology recommends cholinesterase inhibitors (CheIs) and memantine for the treatment of AD; however, these drugs have been suggested for use in patients with DLB and PDD as well (9). In patients with VaD, the treatment is more directed toward the prevention of secondary adverse outcomes, such as stroke, with cardiovascular medication (9). The treatment regimen for FTD is still to be established (9).

Increasing evidence shows that diabetes is a risk factor for AD and VaD (10,11). On the other hand, the nature of the association between PDD and DLB remains unclear (12,13). Diabetes has been suggested to play a role in FTD (14), but further studies are needed. Overall, diabetes seems to be linked to a variety of factors in the pathogenesis of dementia, but the specific connections in individual types of dementia remain to be described in detail.

The majority of studies focus on the prospective risk of dementia in patients with diabetes (11). However, there were 46 million people already living with dementia in 2015 (15), and a recent review (16) estimated the prevalence of diabetes in dementia patients to be 13–20%. Such a large cohort of patients is rarely studied in detail, and characterizing these patients, their demography, and clinical differences (e.g., social status, cognitive status) in types of dementia could have implications for diabetes and dementia. Moreover, there are no comprehensive guidelines for treatment when both of these diseases are present. The recent guidelines for the treatment of elderly patients with type 2 diabetes (17) mainly provide clinical advice on adjusting glycemic targets and exercising caution with regard to polypharmacy when dementia is present. The importance of pharmacovigilance in patients with diabetes who have dementia should not be underestimated; for example, deterioration of diabetes control is associated with certain psychotropic drugs (e.g., antipsychotic agents) used to treat BPSD (9,18). On the other hand, whether the prescription of dementia medication in diabetes patients is different in patients without diabetes has yet to be clarified.

We aimed to elucidate whether among people with dementia there is a difference in dementia subtypes and dementia treatment among those with and those without diabetes. In addition, we wanted to determine the associations of diabetes with regard to specific sociodemographic and clinical determinants in patients with specific dementia disorders.

RESEARCH DESIGN AND METHODS

Study Population

We conducted a cross-sectional study on dementia patients registered in the Swedish Dementia Registry (SveDem) from 2007 until 2012. Data on patients' comorbidities and drug usage were derived from the Swedish Patient Register and the Swedish Prescribed Drug Register and were merged with SveDem data by the National Board of Health and Welfare. The Swedish Patient Register covers inpatient and specialized outpatient care (excluding primary care) in Sweden. The diagnoses are coded according to the ICD-10 (19) and registered at discharge as one main diagnosis, plus up to 21 additional diagnoses (20). The Swedish Prescribed Drug Register, established in July 2005, contains information on all prescribed drugs dispensed at Swedish pharmacies to the entire Swedish population (21).

Dementia

SveDem is a Swedish national quality register created in 2007 to improve the quality of dementia care in Sweden (22). The patients are registered into SveDem either in a primary care unit or in a specialist clinic. In 2012, 58 specialist memory clinics (93% of all in Sweden) and 659 primary care units (60% of all in Sweden) were affiliated with SveDem. Once affiliated, the care unit agrees to report all newly diagnosed dementia patients to SveDem for registration. There are no exclusion criteria, and any patient with newly diagnosed dementia can be registered. Informed consent is not required upon registration. Nevertheless, patients are informed orally and in writing about the registration into SveDem and have the right to refuse participation or withdraw their data from the registry at any time. SveDem does not record the number of patients who refuse participation. A copy of the registered information can be obtained at any time if requested. The estimated coverage of incident dementia cases in Sweden in 2012 was 36% (22). Age, sex, demographic data, BMI, Mini-Mental State Examination (MMSE) scores, diagnostic procedures, type of dementia disorder, treatment, and support are recorded in the register.

Dementia is diagnosed according to the ICD-10 as early-onset AD, late-onset AD, mixed dementia, VaD, unspecified dementia, and other dementia types. In addition, DLB is diagnosed using the criteria of McKeith et al. (23), the Lund-Manchester criteria (24) are used for diagnosis of FTD, and criteria recommended by the Movement Disorder Society (25) are used for the diagnosis of PDD. In this study, the diagnosis of AD included both early-onset and late-onset AD. A diagnosis of unspecified dementia is used when the origin of the dementia is unknown and/or the diagnostic procedures used to differentiate between dementia diagnoses are not sufficient to reach a diagnosis. "Other dementias" include rare disorders such as normal-pressure hydrocephalus or alcohol-induced dementia. To increase the focus of our study, we excluded the other dementias group.

Diabetes

For the diagnosis of diabetes, information from the Swedish Patient Register and the Swedish Prescribed Drug Register was combined. Diabetes was defined by the ICD-10 code E10–E13 when present at any position (main diagnosis or additional diagnoses) in the Swedish

Patient Register between 1 January 2000 and 31 December 2012. Additionally, we also defined diabetes by the administration of antidiabetic drugs (Anatomical Therapeutic Chemical code A10) in the Swedish Prescribed Drug Register from up to 3 years before and up to 3 years after the diagnosis of dementia.

The complications of diabetes were identified in the Swedish Patient Register by ICD-10 codes E10.2–E10.8, E11.2–E11.8, E12.2–E12.8, and E13.2–E13.8 when present at any position (main or additional diagnoses) in the Swedish Patient Register between 1 January 2000 and 31 December 2012.

Hypertension, Obesity, and Dyslipidemia

Hypertension, obesity, and dyslipidemia were defined by ICD-10 codes I10, E66, and E78, respectively, when present at any position (main or additional diagnoses) in the Swedish Patient Register between 1 January 2000 and 31 December 2012.

Drugs

Data on drugs dispensed between 1 July 2005 and 31 August 2013 were extracted from the Swedish Prescribed Drug Register. The drugs were classified according to the Anatomical Therapeutic Chemical classification and defined as follows: insulin (A10A), oral antidiabetic drugs (OADs; A10B), antithrombotic drugs (B01AA03, B01AC06, N02BA01, N02BA51, and B01AC04), cardiac drugs (C01A, C01B, C01C, and C01D), antihypertensive drugs (C02, C03, C07, C08, C09, C09A, C09B, C09C, and C09D), statins (C10AA), antipsychotics (N05A), anxiolytics (N05B), hypnotics/sedatives (N05C), antidepressants (N06A), ChEIs (N06DA), and memantine (N06DX01). Drug prescriptions were identified at seven time points: at the date of dementia diagnosis and in 1-year intervals 3 years before and after that date. Prescription was counted if the drug was present at least once at any of these seven time points. To determine the usage of insulin and OADs concurrently, the prescription was counted only if both drugs were present within one individual time point. The total number of drugs at the time of dementia diagnosis was used as a proxy for overall comorbidity (26).

Statistical Analysis

After excluding patients with "other dementias," reregistrations, and missing information in other registries, 29,630 patients registered between 1 May 2007 and 31 December 2012 were included (Supplementary Fig. 1).

Descriptive data were presented as the mean (SD) or median (interquartile range). Normality of data distribution was checked visually and using the Kolmogorov-Smirnov test. The χ^2 test was used to compare the frequency of nominal variables between two groups. For continuous variables, we used independent-sample *t* test or ANOVA. We used nonparametric equivalents of these tests where the conditions for parametric tests were not fulfilled. Multivariable binary logistic regression (with diabetes as a dependent variable) was used to calculate odds ratios (ORs) with 95% and 99% CIs for associations of patient characteristics with diabetes. We used the following models: model 0 was not adjusted; model 1 included sociodemographic (age, sex, cohabitation, and place of residence) and clinical (registration unit, total number of drugs, MMSE score, and type of dementia) characteristics; and model 2 was adjusted for sociodemographic and clinical characteristics and cardiovascular (antithrombotics, cardiac drugs, antihypertensives, and statins), psychotropic (antipsychotics, anxiolytics, hypnotics/sedatives, and antidepressants), and dementia (ChEIs and memantine) medications. AD was used in models as the reference group for comparison between dementia types. Further, we performed a separate analysis to explore the associations of dementia treatment with diabetes when stratified by specific dementia types. The following models were used: model 0 was nonadjusted; model 1 included sociodemographic and clinical characteristics; and model 2 included sociodemographic characteristics, clinical characteristics, and cardiovascular and psychotropic medications.

To avoid type I error inflation, we used a conservative measure—the Bonferroni correction—to adjust the threshold for significant differences in the univariate analysis and associations in the regression models. The conventional threshold for statistical significance ($P = 0.05$) was divided by the number of comparisons or independent variables entered into the regression models. This adjusted *P* value was used as a measure of significant difference/association.

Data were analyzed using IBM SPSS Statistics for Windows, version 23 (IBM Corp., Armonk, NY)

Ethical Considerations

This study complies with the Declaration of Helsinki and was approved by the regional ethical review board in Stockholm, Sweden (ethical approval number: 2013/147–31/2. The data were deidentified before analysis, and no connection could be made to an individual.

RESULTS

Characteristics of the Patients

Of the 29,630 dementia patients in SveDem, 4,881 (16.5%) had received a diagnosis of diabetes. At the time of dementia diagnosis, the diabetes group was younger (78.8 vs. 79.5 years of age, $P < 0.001$), with fewer females (51.5% vs. 60.9%, $P < 0.001$) and slightly lower global cognitive status (MMSE scores 20.9 vs. 21.2, $P = 0.001$).

In patients with diabetes, the frequencies of AD (23.5% vs. 34.2%, $P < 0.001$), DLB (1.3% vs. 2.4%, $P < 0.001$), and PDD (0.9% vs. 1.6%, $P < 0.001$) were lower than in patients without diabetes. On the other hand, VaD (26.9% vs. 16.9%, $P < 0.001$) and mixed dementia (20.7% vs. 18.6%, $P = 0.001$) were more frequent in patients with diabetes. There was no difference in the frequency of FTD (1.6% vs. 1.6%, $P = 0.946$) and unspecified dementia (25% vs. 24.7%, $P = 0.587$). The group with diabetes more frequently experienced hypertension (67.3% vs. 41%, $P < 0.001$), dyslipidemia (23.5% vs. 9.8%, $P < 0.001$), and obesity (3.3% vs. 0.4%, $P < 0.001$). Further demographic and clinical characteristics are shown in Table 1.

Treatment

Overall, patients with diabetes with dementia were prescribed more drugs (7 vs. 4, $P < 0.001$). In the group of patients with diabetes, antithrombotic (76.7% vs. 56.6%, $P < 0.001$), cardiac (28.1% vs. 18.2%, $P < 0.001$), antihypertensive (88.7% vs. 68.4%, $P < 0.001$), and statin (60.3% vs. 29.9%, $P < 0.001$) drugs were used more frequently than in patients with dementia who did not have diabetes. On the other hand, the use of ChEIs (36.3% vs. 46.7%, $P < 0.001$) and memantine (15% vs. 19.4%, $P < 0.001$) occurred less frequently in the diabetes group.

Insulin-only treatment was prescribed to 851 patients with diabetes (17.4%), 1,816 patients used only OADs (37.2%), 872 patients (17.9%) used insulin and OADs at the same time, and 861 patients (17.6%) had no prescribed pharmacological treatment for diabetes. Insulin-only

Table 1—Characteristics of the study population (n = 29,630)

	Diabetes		
	Yes (n = 4,881)	No (n = 24,749)	P value
Sociodemographic characteristics			
Age, years, mean (±SD)	78.8 (±7.3)	79.5 (±8)	<0.001*
Female sex, *n* (%)	2,516 (51.5)	15,080 (60.9)	<0.001*
Living alone, *n* (%)	2,025 (45.5)	10,936 (47.9)	0.004
Institutionalized, *n* (%)	583 (12)	2,604 (10.6)	0.003
Clinical characteristics			
Registered at memory clinics, *n* (%)	3,097 (63.5)	16,288 (65.8)	0.002
MMSE, mean (±SD)	20.9 (±5.1)	21.2 (±5)	0.001*
Total number of drugs, median (IQR)	7 (5)	4 (5)	<0.001*
Dementia disorder, *n* (%)			
AD	1,148 (23.5)	8,455 (34.2)	<0.001*
Mixed	1,011 (20.7)	4,599 (18.6)	0.001*
VaD	1,312 (26.9)	4,192 (16.9)	<0.001*
DLB	64 (1.3)	589 (2.4)	<0.001*
FTD	79 (1.6)	408 (1.6)	0.946
PDD	45 (0.9)	402 (1.6)	<0.001*
Unspecified	1,222 (25)	6,104 (24.7)	0.587
Hypertension, *n* (%)	3,283 (67.3)	10,271 (41.5)	<0.001*
Obesity, *n* (%)	160 (3.3)	102 (0.4)	<0.001*
Dyslipidemia, *n* (%)	1,145 (23.5)	2,435 (9.8)	<0.001*
Diabetes complications, *n* (%)	2,094 (42.9)		
Treatment, *n* (%)			
Antithrombotics	3,745 (76.7)	14,002 (56.6)	<0.001*
Cardiac drugs	1,370 (28.1)	4,497 (18.2)	<0.001*
Antihypertensives	4,331 (88.7)	16,923 (68.4)	<0.001*
Statins	2,944 (60.3)	7,403 (29.9)	<0.001*
Antipsychotics	751 (15.4)	3,532 (14.3)	0.044
Anxiolytics	1,307 (26.8)	6,178 (25)	0.008
Hypnotics/sedatives	1,737 (35.6)	8,370 (33.8)	0.018
Antidepressants	2,232 (45.7)	11,143 (45)	0.37
ChEIs	1,774 (36.3)	11,547 (46.7)	<0.001*
Memantine	734 (15)	4,812 (19.4)	<0.001*
Insulin only	851 (17.4)		
OADs only	1,816 (37.2)		
OADs and insulin	872 (17.9)		
No antidiabetic drugs	861 (17.6)		

IQR, interquartile range. In the analysis, the threshold for significant differences was corrected for the number of comparisons, and a P value of 0.002 was considered to be significant. *$P < 0.002$.

treatment was most frequently prescribed in patients with VaD (20.2%), unspecified dementia (17.6%), and DLB (17.2%) (Table 2). An OAD-only regimen occurred most frequently in patients with FTD (49.4%), AD (39.8%), and unspecified dementia (38.9%). The combination of insulin and OADs was used most frequently in patients with VaD (19.7%), unspecified dementia (19.6%), and mixed dementia (17.8%). Patients without any prescribed antidiabetic drugs were most often represented in the PDD (24.4%), DLB (21.9%), FTD (21.5%), and AD (21.3%) groups.

Multivariate Analysis

In the fully adjusted logistic regression model (Table 3, model 2), we found that patients with diabetes were significantly more likely to be male (OR 1.41; 99% CI 1.27–1.55) and to receive a higher number of drugs (OR 1.15; 99% CI 1.13–1.17). Dementia patients with diabetes were significantly younger (OR 0.97; 99% CI 0.97–0.98) with lower MMSE score at the time of dementia diagnosis (OR 0.98; 99% CI 0.97–0.99) compared with those without diabetes. When compared with AD, mixed dementia (OR 1.21; 99% CI 1.06–1.39) and VaD (OR 1.17; 99% CI 1.01–1.36) had the strongest association with diabetes. On the other hand, DLB (OR 0.64; 99% CI 0.44–0.94) and PDD (OR 0.45; 99% CI 0.28–0.75) were negatively associated with diabetes. In the unadjusted model, we found that the usage of antipsychotic drugs was more prevalent in patients with diabetes (OR 1.09; 95% CI 1.01–1.19), but this association was not significant in the fully adjusted model (OR 1.08; 99% CI 0.93–1.24). Treatment with hypnotic agents/sedative agents was more prevalent in patients with diabetes in the unadjusted analysis (model 0: OR 1.08; 95% CI 1.01–1.15), but after adjustment for the total number of drugs, we found lower usage of hypnotic drugs/sedative drugs in patients with diabetes (OR 0.82; 99% CI 0.73–0.91). Similarly for antidepressant drugs, we found no significant association with diabetes in the unadjusted model (OR 1.03; 95% CI 0.97–1.09), but the presence of antidepressant drugs was lower in patients with diabetes when adjusted for total number of drugs (OR 0.85; 99% CI 0.77–0.94). The use of ChEIs (OR 0.77; 99% CI 0.69–0.85) and memantine (OR 0.78; 99% CI 0.68–0.89) was less prevalent in patients with diabetes. When we stratified the analysis by the type of dementia disorder (Table 4), we found that patients with diabetes were less likely to receive ChEIs when they received a diagnosis of AD (model 2: OR 0.78; 99% CI 0.63–0.95), mixed dementia (OR 0.69; 99% CI 0.56–0.85), and VaD (OR 0.68; 99% CI 0.49–0.95). Patients with diabetes were less likely to receive memantine for the treatment of AD (OR 0.68; 99% CI = 0.54–0.85) and unspecified dementia (OR 0.70; 99% CI 0.50–0.97).

CONCLUSIONS

We found that diabetes was associated with several demographic and clinical characteristics among dementia patients. Specifically, patients with diabetes received a diagnosis of dementia earlier, had less frequent usage of dementia drugs and specific psychotropic medications, and had a lower presence of DLB and PDD.

The global prevalence of diabetes in people older than age 20 years is estimated to be 8.8% (3). The proportion of patients with diabetes in our study was 16.5%, which corroborates the findings stated in the recent review focusing on dementia comorbidities (13–20%) (16) as well as the diabetes prevalence reported in Swedish individuals >65 years of age (15.6%) (27). In our study, patients with diabetes were slightly younger at the time of dementia diagnosis than those with dementia who did not have diabetes. Diabetes may accelerate the course of cognitive decline (4), resulting in an earlier manifestation of dementia. Another plausible explanation could be that patients with diabetes have more frequent checkups, creating more opportunities by

Table 2—Treatment of diabetes in specific dementia disorders

	Insulin only, *n* (%)	OADs only, *n* (%)	OADs and insulin, *n* (%)	No intervention, *n* (%)
AD (*n* = 1,148)	170 (14.8)	457 (39.8)	174 (15.2)	245 (21.3)
Mixed (*n* = 1,011)	172 (17)	362 (35.8)	180 (17.8)	200 (19.7)
VaD (*n* = 1,312)	265 (20.2)	443 (33.8)	258 (19.7)	194 (14.8)
DLB (*n* = 64)	11 (17.2)	24 (37.5)	9 (14.1)	14 (21.9)
FTD (*n* = 79)	9 (11.4)	39 (49.4)	7 (8.9)	17 (21.5)
PDD (*n* = 45)	9 (20)	16 (35.6)	4 (8.9)	11 (24.4)
Unspecified (*n* = 1,222)	215 (17.6)	475 (38.9)	240 (19.6)	180 (14.7)
P value (χ^2 test)	0.022	0.008	0.005*	<0.001*

P value represents the overall difference in the analyzed drug groups. In the analysis, the threshold for significant differences was corrected for the number of comparisons, and a *P* value of 0.007 was considered to be significant. **P* value <0.007.

the health care system to notice cognitive impairment. The majority of all patients with diabetes were women, but the proportion of women was significantly lower in the diabetes group. This finding is most likely a combination of womens' longer life expectancy (28) and the higher prevalence of diabetes in men (29). We consider the small significant difference in MMSE scores in patients with diabetes and those without diabetes to probably be clinically irrelevant. However, many of the patients registered in SveDem received a diagnosis of dementia during recent years (22), so an accelerated cognitive deterioration in the diabetes group may become relevant in the future follow-ups.

Table 3—ORs with CIs for associations of patients' characteristics with diabetes

	Model 0, ORs (95% CI)	Model 1, ORs (99% CI)	Model 2, ORs (99% CI)
Age	0.99 (0.96–0.99)*	0.97 (0.97–0.98)**	0.97 (0.97–0.98)***
Male sex	1.47 (1.38–1.56)*	1.56 (1.41–1.72)**	1.41 (1.27–1.55)***
Institutional living	1.15 (1.05–1.30)*	0.88 (0.70–1.11)	0.93 (0.74–1.18)
Living alone	0.91 (0.85–0.97)*	1.07 (0.97–1.18)	1.10 (0.99–1.22)
Registered at memory clinic	0.90 (0.85–0.96)*	0.87 (0.78–0.97)**	0.94 (0.84–1.05)
Total number of drugs	1.18 (1.17–1.19)*	1.19 (1.18–1.21)**	1.15 (1.13–1.17)***
MMSE	0.99 (0.98–0.99)*	0.98 (0.97–0.99)**	0.98 (0.97–0.99)***
AD	Reference	Reference	Reference
Mixed	1.62 (1.48–1.78)*	1.46 (1.28–1.67)**	1.21 (1.06–1.39)***
VaD	2.31 (2.11–2.52)*	1.72 (1.51–1.96)**	1.17 (1.01–1.36)***
DLB	0.80 (0.61–1.04)	0.59 (0.40–0.86)**	0.64 (0.44–0.94)***
FTD	1.43 (1.11–1.83)*	1.24 (0.85–1.80)	1.12 (0.76–1.65)
PDD	0.82 (0.60–1.13)	0.40 (0.24–0.65)**	0.46 (0.28–0.75)***
Unspecified	1.47 (1.35–1.61)*	1.23 (1.07–1.42)**	1.08 (0.93–1.25)
Antithrombotics	2.53 (2.36–2.72)*		1.18 (1.05–1.33)***
Cardiac drugs	1.76 (1.64–1.89)*		0.92 (0.82–1.03)
Antihypertensives	3.64 (3.32–4.00)*		1.96 (1.67–2.27)***
Statins	3.56 (3.34–3.80)*		2.29 (2.07–2.54)***
Antipsychotics	1.09 (1.01–1.19)*		1.08 (0.93–1.24)
Anxiolytics	1.10 (1.03–1.18)*		1.03 (0.91–1.15)
Hypnotics/sedatives	1.08 (1.01–1.15)*		0.82 (0.73–0.91)***
Antidepressants	1.03 (0.97–1.09)		0.85 (0.77–0.94)***
ChEIs	0.65 (0.61–0.70)*		0.77 (0.69–0.85)***
Memantine	0.73 (0.67–0.80)*		0.78 (0.68–0.89)***

Age, MMSE score, and total number of drugs were analyzed as continuous variables. Model 0 is not adjusted; model 1 is adjusted for sociodemographic and clinical characteristics; model 2 is adjusted for sociodemographic characteristics, clinical characteristics, and cardiovascular, psychotropic, and dementia medications. The threshold for significance was corrected for the number of independent variables entered in each model. A *P* value of 0.05 was considered significant for model 0, a *P* value of 0.004 was considered significant for model 1, and a *P* value of 0.002 was considered significant for model 2. **P* value <0.05 (model 0). ***P* value <0.004 (model 1). ****P* value <0.002 (model 2).

Diabetes was most common in patients with mixed dementia and VaD, probably due to common pathogenetic mechanisms and shared metabolic and vascular risk factors (30,31), whereas diabetes was less frequently present among DLB and PDD patients. The research focused on diabetes, Parkinson disease (PD), and PDD is quite inconclusive. Scigliano et al. (32) suggested that reduced sympathetic activity in PD could explain the lower presence of diabetes in PD patients. On the other hand, a study by Yang et al. (33) found an increased risk of PD in diabetes patients, and Xu et al. (34) described no significant association between diabetes and PDD.

We consider sex to be a main confounder for DLB and PDD in the nonadjusted model, as these dementia types are more common in men (34–36). Additionally, we propose that the negative association between diabetes and PDD in the adjusted models could be a result of at least two factors. A recent meta-analysis (37) of eight studies found that PD patients in whom dementia develops had particularly high mortality. The presence of diabetes as another major comorbidity could additionally decrease the patients' survival, resulting in lower representation of patients with diabetes and PDD in our study and subsequent negative association between diabetes and PDD. Second, our models compared patients with a specific dementia type to patients with AD. The association could consequently be slightly different when comparing dementia patients to healthy individuals, because diabetes patients already have an increased risk of AD. Therefore, the association among diabetes, PDD, and DLB (which exhibits features that are in common with PDD) (38) remains to be conclusively determined.

A recent study (39) focusing on antidiabetic treatment among elderly Italian people >65 years of age reported similar percentages of insulin-only treatment (15.7%) and OAD-only treatment (38.6%) compared with our study. Compared with the Italian study (9.3%), the use of combined insulin/OAD therapy reported by our study (17.9%) is relatively

Table 4—Associations of dementia drugs with diabetes in individual dementia diagnoses

	Model 0, ORs (95% CI)	Model 1, ORs (99% CI)	Model 2, ORs (99% CI)
AD (*n* = 9,603)			
ChEIs	0.80 (0.70–0.91)*	0.79 (0.65–0.97)**	0.78 (0.63–0.95)***
Memantine	0.70 (0.60–0.81)*	0.70 (0.56–0.88)**	0.68 (0.54–0.85)***
Mixed (*n* = 5,610)			
ChEIs	0.76 (0.66–0.87)*	0.70 (0.57–0.86)**	0.69 (0.56–0.85)***
Memantine	0.96 (0.82–1.12)	0.88 (0.70–1.10)	0.86 (0.69–1.09)
VaD (*n* = 5,504)			
ChEIs	0.68 (0.55–0.86)*	0.64 (0.46–0.89)**	0.68 (0.49–0.95)***
Memantine	1.02 (0.80–1.30)	0.98 (0.69–1.41)	0.99 (0.69–1.43)
DLB (*n* = 653)			
ChEIs	1.37 (0.75–2.51)	1.44 (0.56–3.70)	1.49 (0.56–3.98)
Memantine	0.79 (0.44–1.37)	0.58 (0.25–1.36)	0.71 (0.29–1.72)
FTD (*n* = 487)			
ChEIs	0.40 (0.14–1.15)	0.50 (0.12–2.14)	0.50 (0.11–2.16)
Memantine	0.63 (0.21–1.84)	0.45 (0.08–2.48)	0.36 (0.06–2.10)
PDD (*n* = 447)			
ChEIs	0.71 (0.38–1.33)	0.67 (0.25–1.74)	0.75 (0.27–2.10)
Memantine	0.96 (0.47–1.96)	0.94 (0.30–2.90)	0.84 (0.26–2.72)
Unspecified (*n* = 7,326)			
ChEIs	0.90 (0.79–1.03)	0.89 (0.73–1.10)	0.87 (0.71–1.08)
Memantine	0.74 (0.60–0.91)*	0.72 (0.52–0.99)**	0.70 (0.50–0.97)***

Model 0 is nonadjusted; model 1 is adjusted for sociodemographic and clinical characteristics (excluding dementia type); and model 2 is adjusted for sociodemographic characteristics, clinical characteristics (excluding dementia type), and cardiovascular and psychotropic medications. The threshold for significance was corrected for the number of independent variables entered in each model. A *P* value of 0.05 was considered significant for model 0, a *P* value of 0.006 was considered significant for model 1, and a *P* value of 0.003 was considered significant for model 2. **P* value <0.05 (model 0). ***P* value <0.006 (model 1). ****P* value <0.003 (model 2).

high. On the other hand, the Swedish National Diabetes Register report from 2013 stated a 16.2% usage of combined insulin/OAD therapy in primary care settings but states that the majority of patients with type 2 diabetes receive regular insulin treatment 15 years after the onset of diabetes (39). We propose that this trend could be a factor contributing to the relatively higher usage of the insulin/OAD combination therapy in our cohort, especially when considering the mean age of diabetes onset in Sweden (62.8 years) (40) and the high mean age of patients with diabetes (78.8 years) in our study.

No significant difference was recorded in antipsychotic drug usage in either the univariate analysis or the fully adjusted regression model. Interestingly, the use of antidepressants and hypnotics/sedatives was negatively associated with diabetes in the adjusted model, even though the differences were insignificant or small in the univariate analysis. Patients with diabetes have a higher drug burden, and physicians might be reluctant to prescribe psychotropic drugs for patients with diabetes, fearing the risk of polypharmacy or worsened diabetes control. In addition, the studied interval of drug usage (3 years before and after dementia diagnosis) could be too short to record all drugs used to treat BPSD, subsequently undervaluing the association.

Our study suggests that patients with diabetes are less commonly prescribed ChEIs and memantine. AD is the only indication for ChEIs and memantine usage in Sweden; therefore, the lower number of prescriptions might be attributed to nonindications in patients with VaD and mixed dementia. However, this is not the only explanation, as the negative association remained significant in the analysis stratified by dementia type and survived the adjustment for confounders as well. This stratified analysis showed that patients in whom diabetes and AD are diagnosed were 22% less likely to receive ChEIs and 32% less likely to receive memantine. Evidence that the connection between diabetes and AD is in part due to cerebrovascular disease (41) could lead to a discussion about whether the usage of ChEIs in diabetes patients is warranted. However, diabetes has been shown to affect many metabolic pathways leading to AD pathology (10); therefore, to assume that ChEIs do not provide any benefit to patients with diabetes is premature. Considering the extensive clinical experience with ChEIs (9) and their protective effects on cardiovascular disease in dementia patients (42), we suggest that patients with diabetes with AD should be treated with ChEIs, especially as there currently are no other dementia drugs available (9).

Future studies should concentrate on metabolic control in patients with diabetes with dementia, stratify the patients according to diabetes type, and clarify whether the lower level of dementia treatment in AD patients with diabetes leads to lower long-term cognitive performance or decreased survival.

Limitations and Strengths

Our study has several limitations. The study is observational; therefore, we cannot prove causal relationships. We did not distinguish among different types of diabetes; however, the majority of patients have type 2 diabetes. The diagnosis of dementia was established clinically and was not validated by pathological examination. Also, the nationwide registers that we used lack data on metabolic parameters such as hemoglobin A_{1c} levels, blood pressure, and lipid profile, which could have improved the accuracy of our findings. Nevertheless, we used surrogate information such as hypertension, obesity, dyslipidemia, and complications of diabetes from the Swedish Patient Registry to overcome the dearth of such information. The relatively low national coverage of SveDem (36% in total in Sweden 2012) could affect the representativeness of our study. SveDem includes only incident dementia case patients registered by primary care units or specialist clinics and does not include patients who have received a diagnosis of dementia in nursing homes or in hospitals without subsequent referral to a specialist. This can bias our results, although it is not clear in which direction. However, other studies (43) have found that the patients registered to a quality register were more likely to be male, younger, and healthier, and to have a higher socioeconomic status. This can apply to SveDem as well and might bias the generalizability of our results toward a healthier group of patients,

subsequently underestimating the true frequencies of diabetes and comorbidities. As stated in the SveDem yearly report, the aforementioned 36% may be an underestimation of the total coverage, as the incidence of dementia has decreased since dementia prevalence has been estimated. The coverage is expected to increase with more primary care units and nursing homes joining SveDem in the next years. The monitoring of data in SveDem has been examined, especially in memory clinics, and was in good agreement with medical records.

This study is strengthened by the large sample size of dementia patients and the inclusion of less frequent dementia disorders. SveDem represents the real-world clinical settings and is a valuable source for policy making and health care recommendations. Data from the Swedish Prescribed Drug Register reflect the filling of patient prescriptions and provide information on obtaining the drug but less information on compliance. Additionally, the validity of the Swedish Patient Registry has been shown to be satisfactory for the comorbidities of dementia included in our study (20). The data in the Prescribed Drug Register and the Patient Register are additionally strengthened by their complete national coverage.

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