Research article

Statins, cholesterol and cognition at the time of Alzheimer's disease diagnosis: A cross-sectional study from the Swedish registry for cognitive/dementia disorders

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Abstract

Background: Evidence suggests statins may influence cognition in Alzheimer's disease (AD), but specific use patterns in AD patients remain unclear.

Objective: To identify factors influencing statin use in AD and explore associations between statins, cholesterol, and cognition, evaluated with Mini-Mental State Examination (MMSE) at dementia diagnosis.

Methods: A cross-sectional study using data from the Swedish Registry for Dementia and Cognitive Disorders (SveDem) and Stockholm Creatinine Measurements (SCREAM) from 2007 to 2018. Multivariable logistic regression examined associations between baseline characteristics and statin use, while linear regression analyzed relationships between statins, cholesterol levels, and MMSE scores.

Results: We included 3074 AD patients (mean age 78.1 years; 59.4% women), of whom 1028 used statins (79.6% simvastatin, 20.4% atorvastatin). Patients with diabetes mellitus, ischemic heart disease, or stroke had greater odds of receiving statins. Older patients had slightly lower odds of receiving any statin at baseline (simvastatin use OR 0.98, 95% CI 0.97–0.99). Simvastatin users had 0.53 points higher MMSE on average at baseline compared to non-users of statins (se 0.23, $p = 0.021$). Higher low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC) and high-density lipoprotein cholesterol (HDL-C) levels were associated with higher MMSE in non-users of statins, but not in statin users.

Conclusions: Younger AD patients and those with cardiovascular disease were more likely to use statins. Simvastatin use was linked to higher cognitive scores at diagnosis. In non-users, higher LDL-C, TC, and HDL-C levels correlated with better baseline cognitive scores. Longitudinal studies are needed to investigate the effects of statins on cognitive decline in AD.

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Introduction

The global prescription rates of statins, also known as 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, have been increasing over the past few decades. This trend reflects the widespread use of these medications for the prevention of cardiovascular and cerebrovascular diseases driven by expanding clinical guidelines, aging populations, evidence of efficacy and generic availability.[1–3] Statins primarily work by reducing peripheral low-density lipoprotein cholesterol (LDL-C) levels.[4] Additionally, statins have been shown to increase high-density lipoprotein cholesterol (HDL-C) levels by 5–15% through various mechanisms, though the clinical benefit of this effect remains unclear.[5,6] Finally, statins have been associated with a modest decrease in triglycerides levels.[7]

Statins are commonly classified as lipophilic (e.g., simvastatin, atorvastatin) or hydrophilic (e.g., rosuvastatin, pravastatin),[8] a distinction relevant to their potential central nervous system effects. Lipophilic statins are generally more likely to cross the blood-brain barrier (BBB), though other pharmacokinetic factors—such as molecular weight and transporter interactions—also play a role.[9] Notably, simvastatin showed a higher BBB penetration (>25%), while atorvastatin, despite being lipophilic, had limited penetration (<5%), likely due to its size and structure.[9]

Besides cardiovascular effects, statins have attracted significant attention for their potential cognitive effects, both through lipid-lowering and their pleiotropic actions.[8,10,11] Cholesterol plays a key role in brain function, influencing synaptic plasticity and neurotransmission,[12,13] while an alteration of brain cholesterol homeostasis has been linked to Alzheimer's disease (AD).[14] While the peripheral and central cholesterol pools are separated by the blood-brain barrier, they might interact via oxysterol molecules which could affect neurodegeneration.[11] More specifically, peripheral hypercholesterolemia has been linked to elevated levels of the oxysterol 27-hydroxycholesterol (27-OHC) which effluxes to the brain from the periphery.[11] 27-OHC is part of disrupted brain oxysterol homeostasis in AD and may contribute to neurodegeneration.[11,15] Hypercholesterolemia in midlife is a risk factor for Alzheimer's disease (AD)[16,17] and high LDL cholesterol in midlife is recognized as one of the 14 modifiable risk factors which could collectively prevent about 45% of dementia according to the 2024 Lancet standing Commission.[18]

Despite numerous clinical trials and observational cohort studies, the effectiveness of statins in preventing AD or slowing cognitive decline after disease onset remains inconclusive. Reports of mild, reversible short-term cognitive side effects[19,20] prompted the U.S. Food and Drug Administration to issue a warning on statin labelling in 2012.[21] Large clinical trials examining the risk of AD in statin users generally reported a null effect,[22–25] or an adverse effect[26] while more recent trials reported a protective cognitive effect in selected functional domains.[27] A large number of observational studies, systematic reviews and meta-analyses have generally shown a null[28–30] or a protective effect.[31–35] In patients with established AD, clinical trials were probably underpowered and showed a null effect[36,37] or a beneficial effect.[38,39] Some observational studies as well as meta-analyses which examined cognitive decline in established AD did not show a meaningful effect of statin treatment.[40–42]

More recent findings from our group have shown a possible cognitive benefit in patients with AD receiving statins.[43] Studies in animal models reported beneficial effects of lipophilic but possibly low blood-brain barrier-penetrating atorvastatin[9] which protected against amyloid beta induced hippocampal cell damage in a mouse model[44] and improved spatial cognition.[45] Additionally, apolipoprotein E ϵ4 carriers, who have higher peripheral cholesterol and an elevated risk of AD, may also experience cognitive benefits with statin use.[46] The *APOE* ϵ4 allele is associated with a significantly increased risk of AD,[47–49] and higher LDL-C levels,[50] while *APOE* ϵ2 is considered protective for dementia.[51] One ϵ4 allele increases AD risk 3–4-fold and lowers the age of onset of dementia.[52,53] The cognitive effects of statins are complex, with evidence suggesting both beneficial and harmful impacts.[54] Research on brain and animal models, as well as in AD patients, highlights statins' anti-inflammatory, antioxidant, and neuroprotective actions.[54] However, statins may also impair neuronal plasticity and survival.[54] Negative effects on cognition could stem from mitochondrial dysfunction, increased oxidative stress due to reduced coenzyme Q10, and inhibited cholesterol synthesis, which affects myelination and synaptogenesis.[13] Statins' overall impact on cognition likely depends on factors such as pharmacokinetics (potency, blood-brain barrier permeability), length of statin treatment (short- and long-term effects), patient age, comorbidities, genetics, and underlying dementia pathogenesis.[13,55–57]

There is a lack of information on the use and prescription of statins in patients older than 75 years, who often have

comorbidities, polypharmacy and have the highest prevalence of Alzheimer's and mixed dementia. These patients are underrepresented in clinical trials.[58,59] Current recommendations based on international guidelines advise considering statin therapy for primary prevention in older adults, based on individualized assessment of risk factors and potential benefits versus risks.[58,60,61] Statin therapy is recommended for adults with established cardiovascular disease, regardless of age.[58,61] The guidelines emphasize shared decision-making between clinicians and patients, considering individual preferences, comorbidities, and life expectancy.

This study aims to understand statin use and its association with cognition at the time of dementia diagnosis. The aims are 1) to determine which factors predict statin use, and specifically use of simvastatin or atorvastatin, and 2) to explore the association between statin use, peripheral cholesterol and cognition at the time of dementia diagnosis. We hypothesized that younger patients and patients with established cardiovascular disease are more likely to receive statins, adhering to guidelines of statin prescription. Moreover, we hypothesized that users of the lipophilic simvastatin which readily crosses the blood-brain barrier[9] would have better cognitive scores at the time of dementia diagnosis.

Methods

Study design and databases

We conducted a cross-sectional study based on Swedish registries including patients with incident Alzheimer's or mixed dementia (ICD-10 codes F001, G301, F002, and G308) from the Swedish Registry for Dementia and Cognitive Disorders (SveDem) and laboratory measures from the Stockholm Creatinine Measurements (SCREAM) project from 01.01.2007 to 31.12.2018.[62,63] The SCREAM cohort was primarily established to estimate the burden of chronic kidney disease in the region of Stockholm, which houses approximately a quarter of Sweden's total population.[63] SCREAM links healthcare records and includes the complete population residing in the region, with laboratory data available for 67% of adults[62] and more than 90% of residents over 65 years.[63] It also contains comorbidites from primary care, specialist visits and hospitalizations. This registry has previously been linked with other national quality registries utilizing the unique Swedish personal identification number. SveDem is a quality registry, established in 2007 with an aim to improve and monitor the quality of care of patients with dementia in Sweden.[64] From SveDem, we obtained information on type of dementia according to the ICD-10 codes and cognitive evaluation with Mini-Mental State Examination (MMSE) score at diagnosis. From the Swedish Prescribed Drug Registry which includes all dispensation of prescription medications at pharmacies since July 2005,[65] we obtained information on medication use according to their ATC codes. In Sweden, statin prescribing is guided both by international recommendations (such as the ESC/EAS Guidelines for the Management of Dyslipidaemias[66,67]) and by national guidelines and treatment recommendations issued by the National Board of Health and Welfare (Socialstyrelsen) and the Medical Products Agency (Läkemedelsverket). The Longitudinal Integration Database for Health Insurance and Labour Market Studies[68] contributed data on educational levels. The Swedish National Patient Register contains records on hospitalization diagnoses from 1987 and specialized outpatient care from 2001 onwards.[69] Finally, we used data on date and cause of death from the Swedish Cause of Death Register (Figure 1).

Statistical analysis

Statin use was defined as a statin prescription within 6 months before dementia diagnosis. The primary outcomes were 1. Statin use and 2. MMSE score at the time of dementia diagnosis. We included age, sex, education level, year of diagnosis, type of diagnostic unit, coresident status, comorbidities, and comedication as covariates in adjusted models (Supplemental Table 1). Information on peripheral cholesterol levels included measurements of total cholesterol (TC), triglycerides (TG), LDL-C and HDL-C within 6 months before dementia diagnosis but after at least one prescription of simvastatin or atorvastatin. We focused on simvastatin and atorvastatin due to their differing degrees of brain penetration and their extensive evaluation in both preclinical and clinical studies on neurodegeneration. Additionally, they were the most prescribed statins in the Swedish registries we analyzed; other statins and other non-statin lipid-lowering medications were used in only 406 patients, making those comparison groups too small for meaningful analysis.

Continuous variables were described with mean (standard deviation, SD) and categorical variables were reported as counts (percentages, %). Odds ratios (OR) with corresponding 95% confidence intervals (CI) were estimated using multivariable logistic regression models to examine the association of baseline characteristics with simvastatin and atorvastatin use. Separate linear regression models were utilized to examine the association of (1) simvastatin or atorvastatin with MMSE score at baseline, and (2) the association of LDL-C, TC, HDL-C, TG levels with MMSE score at baseline, among non-users, users of simvastatin and atorvastatin. Separate models were calculated for LDL-C, TC, HDL-C, and TG. Models were adjusted for age, sex, coresident status, diagnostic unit, educational level, diagnosis year, comorbidities and medications, and missing cases were coded as a separate category and included in the models.

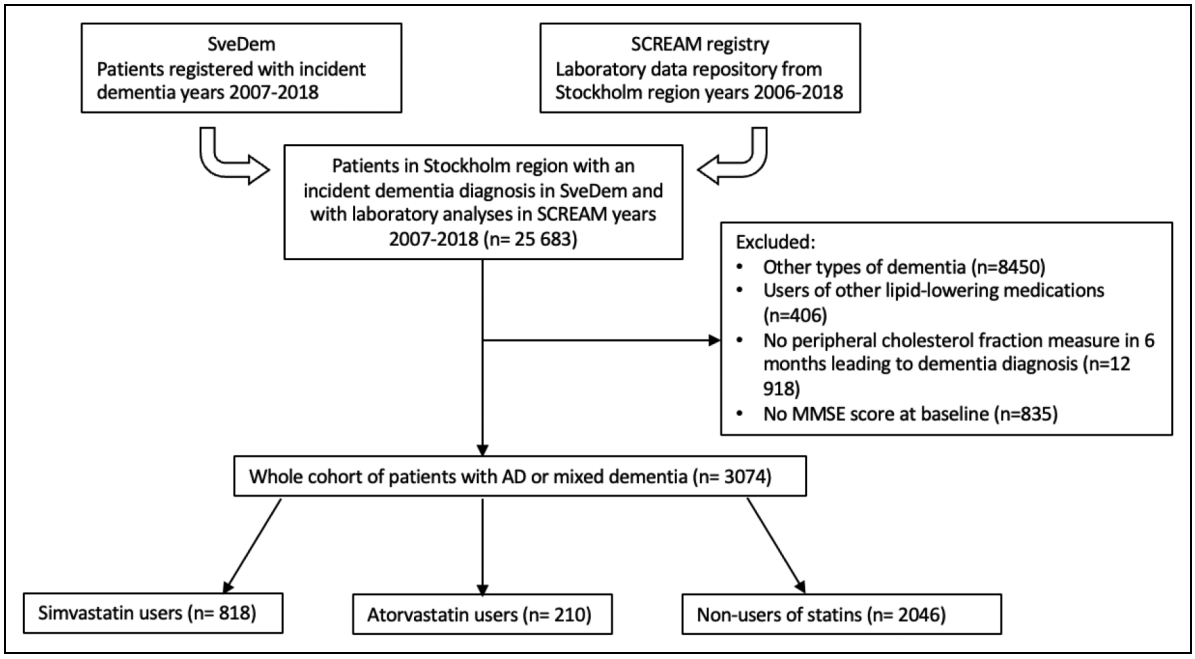

Figure 1. Patient selection flowchart. Our study included patients in the Stockholm region who were registered in SveDem for Alzheimer's disease or mixed dementia from 2007–2018 and had laboratory data available from SCREAM project. We excluded patients with other dementia types, those who did not have MMSE score at diagnosis, patients without cholesterol measures 6 months before dementia diagnosis or patients who used other lipid-lowering medications. Our final cohort consisted of patients with AD or mixed dementia who received simvastatin (n = 818), atorvastatin (n = 210) or did not use statins (n = 2046). SveDem: Swedish Registry for Cognitive/Dementia Disorders; SCREAM: Stockholm Creatinine Measurements Project; MMSE: Mini-Mental State Examination; AD: Alzheimer's disease.

Statistical analyses were performed with SAS, version 9.4 (SAS Institute Inc, Cary, NC) and R 4.2.1 (R Foundation for Statistical Computing). Two-tailed p-values were reported and a value below 0.05 considered significant.

Results

Baseline characteristics of study patients

A total of 3074 AD and mixed dementia patients were included in our study. We identified 818 simvastatin users (79.5% of all statin users), 210 atorvastatin users and 2046 non-users of statins. Distribution of defined daily doses (DDD) of simvastatin and atorvastatin is summarized in Supplemental Table 5. The groups did not differ in age at diagnosis (78.4 ± 6.7, 77.7 ± 6.8, 78.1 ± 8.6, respectively), educational level, or type of diagnostic unit. More patients using atorvastatin had been diagnosed in later years. There was a higher proportion of men among simvastatin users (47.3%), compared to atorvastatin (41.4%) or non-users of statins (37.9%). Simvastatin users had a higher MMSE at diagnosis compared to atorvastatin users or non-users of statins (21.7 ± 4.8, 21.6 ± 4.8, 20.9 ± 5.3). More simvastatin users had a coresident (57.7%, 55.7%, 51.1%). Non-users of statins had higher TC, LDL-C, HDL-C and lower TG. Moreover, a higher proportion of patients who used statins had cardiovascular comorbidities and used other medications to treat comorbid conditions. Detailed information is presented in Table 1.

Factors associated with the use of statins

Older age was associated with lower odds of receiving either simvastatin (OR 0.98, 95% CI 0.97–0.99) or atorvastatin (OR 0.97, 95% CI 0.94–0.99). Diabetes mellitus (OR 2.25, 95% CI 1.79–2.82), stroke (OR 1.75, 95% CI 1.25–2.45) or ischemic heart disease (OR 2.48, 95% CI 1.83–3.35) were associated with greater odds of statin use, whereas congestive heart failure was associated with lower odds of receiving atorvastatin, compared to no statin (OR 0.47, 95% CI 0.25–0.86) (Table 2 and Supplemental Table 3). Analyses stratified by dementia type (AD versus mixed dementia) showed similar results (not presented).

Simvastatin users had 0.53 points higher MMSE at baseline, compared to non-users of statins (se 0.23, $p = 0.021$, adjusted model). Analysis stratified by sex showed 0.73 points higher MMSE in male simvastatin users (se 0.36, $p = 0.042$, adjusted model) whereas female simvastatin users had 0.34 higher MMSE points, which was not statistically significant ($p = 0.261$) (Table 3).

Higher LDL-C, TC and HDL-C levels at baseline were associated with higher MMSE in non-users of statins in

Table 1. Baseline characteristics of study patients.

Variables	Statin nonuser (n = 2 046)	Simvastatin (n = 818)	Atorvastatin (n = 210)
Age at dementia diagnosis, y			
Mean (SD)	78.1 (8.6)	78.4 (6.7)	77.7 (6.8)
< 65	180 (8.8)	26 (3.2)	10 (4.7)
65–75	431 (21.0)	183 (22.3)	52 (24.2)
75–85	944 (45.9)	466 (56.7)	119 (55.3)
≥ 85	500 (24.3)	147 (17.9)	34 (15.8)
Sex			
Male	775 (37.9)	387 (47.3)	87 (41.4)
Female	1271 (62.1)	431 (52.7)	123 (58.6)
Educational level			
Completed compulsory education	629 (30.7)	251 (30.7)	56 (26.7)
Upper secondary	837 (40.9)	342 (41.8)	98 (46.7)
College/university	523 (25.6)	206 (25.2)	55 (26.2)
Missing	57(2.8)	19(2.3)	1 (0.5)
Coresident status			
Cohabiting	1045 (51.1)	472 (57.7)	117 (55.7)
Living alone	949 (46.4)	330 (40.3)	91 (43.3)
Missing	52 (2.5)	16 (2.0)	2 (1.0)
Type of diagnostic unit			
Specialist care	2036 (99.5)	816 (99.8)	208 (99.0)
Primary care	10 (0.5)	2 (0.2)	2 (1.0)
Calendar year of diagnosis			
2007–2009	292 (14.3)	98 (12.0)	9 (4.3)
2010–2012	543 (26.5)	201 (24.6)	13 (6.2)
2013–2015	587 (28.7)	237 (29.0)	41 (19.5)
2016–2018	624 (30.5)	282 (34.5)	147 (70.0)
MMSE score			
Mean (SD)	20.9 (5.3)	21.7 (4.8)	21.6 (4.8)
0–19	677 (33.1)	232 (28.4)	65 (31.0)
20–24	786 (38.4)	333 (40.7)	72 (34.3)
25–30	583 (28.5)	253 (30.9)	73 (34.8)
Comorbidities			
Hyperlipidemia	22 (1.1)	104 (12.7)	42 (20.0)
Hypertension	527 (25.8)	331 (40.5)	89 (42.4)
Diabetes mellitus	215 (10.5)	238 (29.1)	48 (22.9)
Type 1 diabetes mellitus	24 (1.2)	28 (3.4)	7 (3.3)
Type 2 diabetes mellitus	199 (9.7)	221 (27.0)	43 (20.5)
Atrial fibrillation	242 (11.8)	139 (17.0)	49 (23.3)
Angina pectoris	57 (2.8)	68 (8.3)	21 (10.0)
Congestive heart failure	107 (5.2)	83 (10.1)	20 (9.5)
Myocardial infarction	53 (2.6)	92 (11.2)	43 (20.5)
Stroke	95 (4.6)	96 (11.7)	29 (13.8)
Ischemic heart disease	108 (5.3)	155 (18.9)	57 (27.1)
Chronic respiratory disease	100 (4.9)	51 (6.2)	13 (6.2)
Liver disease	9 (0.4)	3 (0.4)	1 (0.5)
Cancer	314 (15.3)	133 (16.3)	41 (19.5)
Fracture	246 (12.0)	99 (12.1)	18 (8.6)
Chronic kidney disease	502 (24.5)	246 (30.1)	55 (26.2)
Alcohol-related diseases	43 (2.1)	15 (1.8)	1 (0.5)
Depression	114 (5.6)	50 (6.1)	10 (4.8)
Medication use			
Cardiac drugs	367 (17.9)	270 (33.0)	75 (35.7)
Antihypertensives	45 (2.2)	26 (3.2)	10 (4.8)
Diuretics	448 (21.9)	268 (32.8)	62 (29.5)
Peripheral vasodilators	44 (2.2)	73 (8.9)	27 (12.9)
Vasoprotective drugs	121 (5.9)	50 (6.1)	26 (12.4)
β-blocking agents	528 (25.8)	451 (55.1)	118 (56.2)

(continued)

Table 1. Continued.

Variables	Statin nonuser (n = 2 046)	Simvastatin (n = 818)	Atorvastatin (n = 210)
Calcium channel blockers	387 (18.9)	244 (29.8)	62 (29.5)
RAAS	633 (30.9)	475 (58.1)	139 (66.2)
Insulin	86 (4.2)	111 (13.6)	26 (12.4)
Other antidiabetics	154 (7.5)	183 (22.4)	39 (18.6)
NSAIDs	138 (6.7)	57 (7.0)	16 (7.6)
Vitamin D	63 (3.1)	26 (3.2)	13 (6.2)
Anticoagulants	201 (9.8)	144 (17.6)	48 (22.9)
Antiplatelets	482 (23.6)	478 (58.4)	114 (54.3)
Anxiolytics	263 (12.9)	92 (11.2)	26 (12.4)
Hypnotics	365 (17.8)	189 (23.1)	52 (24.8)
Antipsychotics	107 (5.2)	28 (3.4)	7 (3.3)
Antidepressants	435 (21.3)	230 (28.1)	54 (25.7)
TC, mmol/L, Mean (SD)	5.5 (1.1)	4.4 (1.0)	4.6 (1.1)
LDL-C, mmol/L, Mean (SD)	3.3 (0.9)	2.4 (0.9)	2.4 (0.9)
HDL-C, mmol/L, Mean (SD)[a]	1.7 (0.5)	1.5 (0.5)	1.6 (0.5)
TG, mmol/L, Mean (SD)[b]	1.2 (0.6)	1.3 (0.6)	1.3 (0.7)

SD: standard deviation; MMSE: Mini-Mental State Examination; RAAS: Agents acting on the renin-angiotensin system; TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL: high-density lipoprotein cholesterol; TG: triglycerides.
[a]n = 1710 for nonuser, n = 670 for simvastatin, n = 147 for atorvastatin; [b]n = 1917 for nonuser, n = 780 for simvastatin, n = 206 for atorvastatin.

Table 2. Factors associated with the use of simvastatin or atorvastatin compared to non-use of statins.

	Simvastatin (n = 818)		Atorvastatin (n = 210)	
Variables	OR (95%CI)	*p*	OR (95%CI)	*p*
Age at dementia diagnosis, y	0.98 (0.97–0.99)	0.005	0.97 (0.94–0.99)	0.002
Sex				
Male	REF		REF	
Female	0.84 (0.69–1.02)	0.076	1.14 (0.82–1.58)	0.434
Educational level				
Completed compulsory education	REF		REF	
Upper secondary	0.86 (0.46–1.58)	0.618	0.19 (0.03–1.48)	0.113
College/university	1.21 (0.94–1.55)	0.144	1.44 (0.94–2.19)	0.092
Missing	1.12 (0.90–1.40)	0.303	1.38 (0.96–2.00)	0.087
Coresident status				
Cohabiting	REF		REF	
Living alone	0.72 (0.38–1.38)	0.328	0.32 (0.07–1.44)	0.137
Missing	0.75 (0.61–0.91)	0.004	0.83 (0.60–1.15)	0.256
Comorbidities				
Diabetes mellitus	2.39 (1.89–3.02)	<0.001	1.73 (1.18–2.54)	0.005
Atrial fibrillation	0.89 (0.67–1.19)	0.442	1.51 (0.98–2.33)	0.064
Congestive heart failure	0.70 (0.47–1.03)	0.068	0.47 (0.25–0.86)	0.014
Stroke	1.71 (1.20–2.42)	0.003	1.98 (1.19–3.29)	0.009
Ischemic heart disease	2.17 (1.58–2.99)	<0.001	3.98 (2.57–6.15)	<0.001
Chronic kidney disease	0.94 (0.75–1.17)	0.578	0.81 (0.56–1.17)	0.264
Medication use				
Diuretics	1.18 (0.95–1.47)	0.144	0.96 (0.67–1.38)	0.832
Peripheral vasodilators	1.93 (1.24–3.00)	0.004	2.74 (1.53–4.91)	0.001
Vasoprotective drugs	0.90 (0.62–1.32)	0.590	2.16 (1.33–3.52)	0.002
β-blocking agents	2.29 (1.86–2.81)	<0.001	1.97 (1.40–2.78)	<0.001
Calcium channel blockers	1.26 (1.02–1.56)	0.033	1.20 (0.85–1.68)	0.305
RAAS	2.09 (1.73–2.54)	<0.001	3.38 (2.44–4.68)	<0.001
Antiplatelets	2.83 (2.32–3.44)	<0.001	2.38 (1.70–3.34)	<0.001
Hypnotics	1.32 (1.04–1.66)	0.022	1.46 (1.00–2.12)	0.048
Antipsychotics	0.54 (0.33–0.87)	0.012	0.47 (0.20–1.11)	0.085
Antidepressants	1.25 (1.00–1.55)	0.047	0.97 (0.68–1.40)	0.884

RAAS: Agents acting on the renin-angiotensin system.

Table 3. Association between statin use and MMSE score at diagnosis.

	Crude model		Adjusted model		Male, adjusted model[a]		Female, adjusted model[b]	
Variables	β (se)	*p*	β (se)	*p*	β (se)	*p*	β (se)	*p*
Nonuser (n = 2 046)	REF		REF		REF		REF	
Simvastatin (n = 818)	0.72 (0.21)	0.007	0.53 (0.23)	0.021	0.73 (0.36)	0.042	0.34 (0.30)	0.261
Atorvastatin (n = 210)	0.67 (0.37)	0.073	0.27 (0.38)	0.475	0.27 (0.61)	0.665	0.31 (0.49)	0.528

Model adjusted for age, coresident status, diagnostic unit, educational level, diagnosis year, comorbidities and medications. MMSE: Mini-Mental State Examination.

[a]n = 775 for nonuser, n = 387 for simvastatin, n = 87 for atorvastatin; [b]n = 1271 for nonuser, n = 431 for simvastatin, n = 123 for atorvastatin.

separate adjusted models (β 0.32 (se 0.13, p = 0.013), 0.47 (se 0.11, p < 0.001), 1.02 (se 0.26, p < 0.001), respectively). The association had a very small effect size and was not statistically significant for simvastatin or atorvastatin users. (Tables 4 and 5). The interaction terms between sex and statin use or sex and cholesterol on MMSE score was not significant.

Discussion

In our nationwide Swedish registry study including patients with AD or mixed dementia, we observed the following key findings: (1) Older patients were less likely to receive simvastatin or atorvastatin, (2) simvastatin users had a better cognition (measured as MMSE score) at the time of diagnosis, compared to non-users of statins, (3) higher LDL-C, TC and HDL-C levels were associated with a better MMSE at baseline in non-users of statins.

In Sweden, simvastatin was prescribed more frequently according to national guidelines considering the cost and benefit, but this has changed in later years, following the international guidelines that advise moderate to high-intensity statin use in cardiovascular disease prevention.[60,61,70] A shift to prescribing atorvastatin from simvastatin has been observed in Sweden in the later years.[71] In our cohort 80% of statin users were taking simvastatin. Patients with ischemic heart disease were more likely to receive statins and were almost four times more likely to receive atorvastatin, reflecting the preference of this statin in patients with atherosclerotic disease. On the other hand, older patients were less likely to be prescribed statins in our study. For every one-year increase in age at dementia diagnosis, the adjusted likelihood of receiving either simvastatin or atorvastatin at baseline decreased by approximately 2%. These results may reflect the decision of prescribing statins in older individuals, based on the balance between the cardiovascular benefits, potential risk for adverse effects, and estimated survival. A large general population study including over 7 million participants in UK reported growing initiation and growing prevalent use of statins in older patients which declined only after age 85.[1] Another study found that people aged 65 to 75 were more likely to receive statins than those younger or older, and high-intensity statins were prescribed more frequently to people 65 and younger, and least frequently to those 75 or older.[3]

In our study, simvastatin users had 0.53 points higher MMSE on average at dementia diagnosis, compared to non-users of statins. Analysis stratified on sex showed the association was driven by men who had 0.73 higher MMSE points compared to male simvastatin non-users, while the association was not significant in women. In our previous study including 15,586 Alzheimer's and mixed dementia patients, we observed a dose-dependent, slower cognitive decline over time in simvastatin users compared to non-users of statins.[43] In the early stages of AD, certain patients may experience disrupted central lipid metabolism and elevated neuroinflammation levels, and treatment with simvastatin could theoretically improve these issues.[54] Simvastatin's ability to cross the blood-brain barrier allows it to exert various neuroprotective actions, including protection against tau phosphorylation,[9] anti-inflammatory effects, promotion of hippocampal neurogenesis as well as enhancement of neurotropic factors.[72] Moreover, atorvastatin demonstrated beneficial cognitive effects in mouse models, which included an improved spatial cognition[45] as well as reversal of hippocampal cell damage by $A\beta_{40}$.[44] However, despite being lipophilic, its brain penetration may be limited due to its large molecular size.[9] Clinical trials involving patients with mild to moderate AD have reported either null effects of simvastatin[36] or atorvastatin[37] or a potential cognitive benefits from simvastatin[39] or atorvastatin treatment[38] with MMSE as an outcome. Additionally, sex-related differences in pharmacokinetics and pharmacodynamics of lipid metabolism statins have been a longstanding topic of debate, influenced by various factors, including hormonal status and its impact on cardiovascular risk profiles.[73–75] Cholesterol serves as the substrate for sex hormone biosynthesis suggesting an influence of statins on sex hormones levels.[76] However, the overall role of testosterone in the brain in cognitive functions is still not clear.[77,78] Most studies did not find a significant effect of statins on serum testosterone levels,[79] though simvastatin has been linked to dose- and duration-

Table 4. The association between LDL-C, TC, HDL-C, TG and MMSE score at diagnosis among non-users, and users of simvastatin and atorvastatin.

	Nonuser		Simvastatin		Atorvastatin	
Variables	β (se)	*p*	β (se)	*p*	β (se)	*p*
Crude model						
LDL-C (n = 2046)	0.43 (0.13)	0.001	0.40 (0.19)	0.038	0.33 (0.35)	0.353
TC (n = 2046)	0.55 (0.11)	<0.001	0.30 (0.16)	0.065	0.34 (0.30)	0.259
TG (n = 1917)[a]	0.06 (0.20)	0.776	0.39 (0.27)	0.159	0.58 (0.49)	0.234
HDL-C (n = 1710)[b]	1.09 (0.24)	<0.001	−0.48 (0.39)	0.219	−0.20 (0.80)	0.798
Adjusted model						
LDL-C (n = 2046)	0.32 (0.13)	0.013	0.11 (0.20)	0.572	0.22 (0.36)	0.545
TC (n = 2046)	0.47 (0.11)	<0.001	0.11 (0.18)	0.518	0.19 (0.31)	0.555
TG (n = 1917)[a]	0.06 (0.20)	0.766	0.38 (0.28)	0.170	0.83 (0.47)	0.081
HDL-C (n = 1710)[b]	1.02 (0.26)	<0.001	−0.30 (0.41)	0.472	−0.25 (0.86)	0.767

[a]n = 1917 for nonuser, n = 780 for simvastatin, n = 206 for atorvastatin; [b]n = 1710 for nonuser, n = 670 for simvastatin, n = 147 for atorvastatin.
Model adjusted for age, sex, education level, coresident status, type of diagnostic unit, calendar year of dementia diagnosis, comorbidities and medications.

Table 5. The association between LDL-C, TC, HDL-C, TG and MMSE score at diagnosis among non-users, and users of simvastatin and atorvastatin, stratified by sex.

	Nonuser			Simvastatin			Atorvastatin		
Variables	n	β (se)	*p*	n	β (se)	*p*	n	β (se)	*p*
Men									
LDL-C	775	0.05 (0.24)	0.837	387	−0.34 (0.32)	0.29	87	0.03 (0.55)	0.960
TC	775	0.19 (0.21)	0.381	387	−0.26 (0.28)	0.357	87	0.14 (0.50)	0.781
TG	734	−0.14 (0.32)	0.670	372	0.06 (0.41)	0.889	86	0.11 (0.69)	0.875
HDL-C	643	1.23 (0.49)	0.013	317	−0.92 (0.64)	0.151	61	0.56 (1.72)	0.747
Women									
LDL-C	1271	0.39 (0.15)	0.011	431	0.32 (0.26)	0.204	123	0.39 (0.51)	0.448
TC	1271	0.53 (0.14)	<.001	431	0.31 (0.23)	0.176	123	0.14 (0.43)	0.739
TG	1183	0.16 (0.26)	0.532	408	0.65 (0.37)	0.081	120	1.56 (0.68)	0.024
HDL-C	1067	0.82 (0.31)	0.009	353	0.12 (0.54)	0.832	86	−0.75 (1.13)	0.509

Model adjusted for age, education level, coresident status, type of diagnostic unit, calendar year of dementia diagnosis, comorbidities and medications.

dependent reductions.[80,81] On the other hand, faster statin metabolism in women, due to higher Cytochrome P450 3A4 activity, may reduce the effectiveness of lipophilic statins like atorvastatin and simvastatin.[74,75] Moreover, we must consider possible epidemiological biases inherent to the design of our study. Notably, we did not differentiate between new and prevalent users of statins due to the small number of new users in this cohort, and this could lead to prevalent-user bias, limiting our findings.

Additionally, higher levels of LDL-C, total cholesterol and HDL-C were associated with better cognitive scores at dementia diagnosis in non-users of statins in our study. While hypercholesterolemia in midlife has been recognized as one of the risk factors for AD in late life,[16] higher levels of cholesterol in late life have been connected to a reduced risk of dementia[82,83] and reflect less frailty and better overall health.[84] High LDL cholesterol may be associated with better cognitive scores in non-users of statins because it could reflect better overall health, non-AD pathologies, nutritional status, or cholesterol's role in brain function in that group. In contrast, statin use by lowering cholesterol without impacting nutrition or frailty, may disrupt the statistical association between cholesterol and cognition.

An interesting study including more than 450,000 participants from the UK biobank cohort investigated cross-sectional and longitudinal associations between statin use and cognitive performance in patients aged 40–69 without dementia.[55] In this study, statin use was associated with negative effects on cognition at baseline through lowering LDL-C (proportion mediated 51.4%). However, after 8 years of follow-up, there was no association between statin use and cognition which may suggest that the long-term use of statins could outweigh these short-term adverse effects by diminishing cardiovascular risk which promotes AD. Moreover, the relationship between LDL-C levels and cognition may be U-shaped as shown in previous research.[85] A Mendelian randomization study by Williams

et al. did not find support for a preventive effect on AD of lowering LDL-C by pathways related to statins, ezetimibe, or PCSK9 inhibitors.[86] In line with our results, this suggests that the rationale for repurposing statins in the cognitive field may be based on mechanisms other than LDL-C lowering. Such pleiotropic mechanisms may include mitigation of inflammation, antioxidative effects or transcriptional effects on genes involved in processes such as cell growth, structure and signaling as well as glucose metabolism.[10,14,55] The variability in statin response, lipid profile variations as well as genetic factors in relation to AD has been further elucidated through pharmacogenetic studies. De Oliveira et al. demonstrated that selected protective variants of *LDLR* and *APOE* were associated with reduced risk of late-onset AD and slower cognitive decline, regardless of cholesterol variations, and that carriers of specific genetic variants benefited from lipophilic statins.[87] In another study, these authors have reported that selected protective variants of *CETP* and *NR1H2* against risk of AD also slowed cognitive and functional decline for *APOE* ϵ4 carriers in particular, regardless of cholesterol variations, while receiving lipophilic statins might affect carriers of specific genetic variants.[88] Moreover, *APOE* haplotypes appears to modulate the effects of lipid profile changes in AD dementia.[89] APOE4- haplotypes may enhance lipid availability to support neuronal membrane integrity with rising cholesterol levels, whereas *APOE* ϵ4 carriers did not show any cognitive effects of lipid profile variations as these patients exhibit less efficient neural repair. In this study, lipophilic statins had non-significant protective effects for *APOE4-* carriers only.[89] In conclusion, these studies allow for a more personalized understanding of lipid profile variations and genetic factors related to cognition as well as the effects of statins on cognitive function in AD patients.[87–89]

The selection of our cohort through combined large national quality Swedish registries is an important strength of our study. However, a few limitations must be noted. Cross-sectional designs can be biased by unmeasured confounding and possible reverse causation, e.g., patients with a better cognition having a higher likelihood of receiving the statins. Moreover, it does not allow to draw any conclusions on cognitive trajectory. Basal concentrations of LDL-C affect the likelihood of receiving statins, which in turn has a treatment-feedback effect on LDL-C. This might have contributed to bias and should be considered in future longitudinal studies. Another limitation is that cholesterol levels were assessed at a single time point within six months prior to diagnosis, which may not reliably reflect long-term lipid profiles. This is particularly relevant in older adults or individuals with advanced disease, where cholesterol levels are more prone to fluctuation. We indirectly assumed patients adhered to medications they obtained from the pharmacies. Moreover, information on duration of statin therapy were not included in our study. Since the medication registry was established in 2005, it is unfortunately not possible to determine from our data whether most patients in our cohort initiated statin therapy during midlife or later. Importantly, the registries we used for our study do not include genetic factors, such as *APOE* haplotypes, or other relevant genetic polymorphisms relevant to the metabolism or transport of statins. Moreover, we did not have the information regarding dietary therapy for these patients. Additionally, a half-point difference on the 30-point MMSE may not be clinically relevant, although it could become relevant over follow-up if effects confound, which we will investigate in future studies. In the future, longitudinal analyses including these factors are warranted to determine the long-term cognitive effects of statins by their cholesterol-lowering effects as well as other potential pathways for further stratification and personalized medicine intervention strategies for AD.

Conclusions

In this study, younger age and cardiovascular comorbidities were associated with higher likelihood of statin prescription. Statin use was associated with higher MMSE scores at the time of dementia diagnosis. In non-users, higher LDL-C, total cholesterol, and HDL-C levels correlated with better baseline cognitive scores. Although limited by cross-sectional design, this study provides valuable insights for designing future longitudinal investigations of statins and cognition. Baseline MMSE is a strong predictor of cognitive decline, and pre-existing differences between treated and untreated patients must be considered when interpreting cognitive trajectories. Additionally, factors influencing statin prescription, as outlined in this paper, are critical both for optimizing treatment and access in dementia populations and for addressing potential confounding in longitudinal cognitive research.

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Ethical considerations

This study complies with the Declaration of Helsinki and was approved by the Swedish Ethical Review Authority (No: 2024-00178-02). All data were pseudonymized to the researchers before analysis.

Consent to participate

Study participants and their caregivers were informed of inclusion in SveDem at registration and had the right to decline the participation. The compulsory registries do not require consent. This study was exempted from written consent by the ethical authority.

Consent for publication

Not applicable.

Author contribution(s)

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Data availability statement

The data is not publicly available due to the Swedish legislation. If researchers are interested in researching on SveDem data, they can contact the SveDem steering committee or the National Board of Health and Welfare (Socialstyrelsen).

Supplemental material

Supplemental material for this article is available online.

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