Statins are associated with a reduced risk of Alzheimer disease regardless of lipophilicity. The Rotterdam Study

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ABSTRACT

Background: Cross-sectional reports suggest that statin users are less likely to have Alzheimer disease (AD). Prospective studies have provided inconsistent evidence. Moreover, it is unclear whether the association differs for lipohilic statins, those that could more easily pass the blood–brain barrier and hydrophilic statins.

Objectives: To prospectively evaluate whether use of statins is associated with the risk of AD, and to determine whether associations differ for lipophilic and hydrophilic statins.

Method: 6992 participants of the prospective, population-based Rotterdam Study were followed, from baseline (1990–1993) until January 2005 for incident AD. Data on all filled prescriptions came from pharmacy records. For each date on which each event occurred, cholesterol-lowering drug use for the person who experienced the event and all remaining persons in the cohort was categorised as "any" or "never" use. A distinction was made between statin, lipophilic and hydrophilic statins, and non-statin cholesterol-lowering drugs. Data were analysed with the Cox regression analysis, adjusting for sex, age and potential confounders.

Results: During follow-up (mean 9 years), 582 persons developed AD. Compared with never use of cholesterol-lowering drugs, statin use was associated with a decreased risk of AD (HR 0.57; 95% CI 0.37 to 0.90), but non-statin cholesterol-lowering drug use was not (HR 1.05; 95% CI 0.45 to 2.44). HRs were equal for lipophilic (HR 0.54; 95% CI 0.32 to 0.89) and hydrophilic statins (HR 0.54; 95% CI 0.26 to 1.11).

Conclusion: In the general population, the use of statins, but not of non-statin cholesterol-lowering drugs, was associated with a lower risk of AD compared with never use of cholesterol-lowering drugs. The protective effect was independent of the lipophilicity of statins.

Cross-sectional observational studies have suggested an association between the use of cholesterol-lowering drugs, particularly 3-hydroxy-3-methylglutaryl-coenzyme-A-reductase inhibitors (statins), and the risk of Alzheimer disease (AD).[1–6] Thus far, the evidence from prospective studies for a protective effect of statins on the risk of AD is less clear and inconsistent.[3 7–13] Important limitations of these studies, however, included use of interview data on drug exposure or cross-sectional exposure assessment, and short duration of follow-up. No clinical trial has yet been reported that investigated the efficacy of statin therapy in preventing AD in persons without cognitive impairment.[14–16]

The mechanism by which cholesterol-lowering drugs may affect Alzheimer pathogenesis is unclear. Since cholesterol is essential for normal function of the brain, the effect of these drugs on serum cholesterol was considered a potential underlying mechanism of action. However, brain cholesterol is synthesised in situ, and exchange with the periphery is prevented by the blood–brain barrier.[17] Hence, it was debated whether lowering of serum cholesterol levels by these drugs could actually affect brain cholesterol homeostasis.[17] This led to the hypothesis that only the lipophilic statins, which could cross the blood–brain barrier more easily, would affect brain cholesterol metabolism.

The Rotterdam Study is a large prospective population-based cohort study with detailed information on drug exposure from pharmacy dispensing records, data on potential confounders and systematic assessment of dementia outcomes.[18] We investigated whether the use of statins or other, non-statin, cholesterol-lowering agents, was associated with the risk of AD. In addition, we determined whether any observed associations differed between lipophilic and hydrophilic statins.

METHODS

Study population

The Rotterdam Study is a prospective, population-based cohort study of age-related disorders.[18] The medical ethics committee of the Erasmus Medical Centre, Rotterdam, The Netherlands, approved the study. Between 1990 and 1993, all persons aged 55 years or older living in Ommoord, a district of Rotterdam, were invited to participate. Of the 10 275 eligible persons, 7983 (78%) signed informed consent. Of these, 7528 (94%) were screened for dementia, and 7046 were found to be free of dementia at baseline.[19] Follow-up examinations, including screening and clinical workup for dementia, were conducted in 1993 to 1994, 1997 to 1999 and 2000 to 2004. In addition, the cohort was continuously monitored for major disease outcomes and death through linkage with records of general practitioners, the Regional Institute for Outpatient Mental Health Care and bimonthly updates from the municipality records. This resulted in a virtually complete follow-up for dementia until 1 January 2005.

Nearly all persons (99.7%) were registered at one or more of seven automated pharmacies serving the Ommoord area. Of these pharmacies, records of all filled prescriptions were available as of 1 January 1991. To ensure at least 6 months' medication history, we excluded persons for whom follow-up

ended before 1 July 1991. Consequently, the study population consisted of 6992 persons.

Assessment of drug exposure

Complete information on all filled prescriptions for all persons was obtained in automated format from the pharmacies. This included the product name; international non-proprietary name; Anatomical Therapeutic Chemical (ATC) code; total number of delivered units (eg, tablets/capsules); prescribed daily number of units; date of delivery and drug dosage. The duration of a prescription is calculated as the total number of delivered units divided by the prescribed daily number of units.

Cholesterol-lowering drugs were classified as statins (simvastatin, pravastatin, fluvastatin, atorvastatin, cerivastatin, rosuvastatin) or non-statin cholesterol-lowering drugs (fibrates, bile acid binding resins or nicotinic acid and derivatives). Statins were further subdivided into lipophilic (simvastatin, atorvastatin, cerivastatin) and hydrophilic statins (pravastatin, fluvastatin, rosuvastatin) based on their relative lipid solubility.[20–23] Lipophilic statins are thought to pass the blood–brain barrier more efficiently than hydrophilic statins, which could be relevant to their effect on Alzheimer pathology.[24–26] All drugs under study are available in The Netherlands only on prescription. In the 1998 Dutch guidelines on the prevention of cardiovascular disease, simvastatin is the statin of first choice for treatment of hypercholesterolaemia, followed by pravastatin.[27]

Diagnosis of AD

The diagnosis of dementia was made following a three-step protocol. Screening was done with the Mini-Mental State Examination (MMSE) and Geriatric Mental State schedule (GMS) organic level for all persons. Screen-positives (MMSE score <26 or GMS organic level >0) underwent the Cambridge examination for mental disorders of the elderly.[28 29] Persons who were suspected of having dementia underwent more extensive neuropsychological testing. When available, imaging data were used. In addition, the total cohort was continuously monitored for incident dementia through computerised linkage between the study database and digitalised medical records from general practitioners and the Regional Institute for Outpatient Mental Health Care. The diagnosis of dementia and subtype of dementia was made in accordance with internationally accepted criteria for dementia (DSM-III-R), AD (NINCDS-ADRDA) and vascular dementia (NINDS-AIREN) by a panel consisting of a neurologist, neurophysiologist and research physician, blinded to drug exposure of the study population.[30–32]

Other covariates

Covariates included age, sex, education level, smoking, total serum cholesterol, body mass index, systolic blood pressure, diabetes mellitus, and cardiovascular and cerebrovascular disease. Education was assessed at the baseline interview and dichotomised into low education (including primary education only or low vocational training) and high education (including intermediate-level vocational training, secondary education or university). Smoking status was also self-reported and categorised as ever or never smoker. Total serum cholesterol was measured in non-fasting blood drawn at baseline. Sitting blood pressure was measured on the right upper arm using a random-zero sphygmomanometer. Diabetes mellitus was defined as a non-fasting or 2 h postload glucose level of ⩾11.1 mmol/l or antidiabetic medication use at baseline. Cardiovascular disease included myocardial infarction, coronary artery bypass graft, percutaneous transluminal coronary angioplasty, atrial fibrillation and heart failure. Cerebrovascular disease included transient ischaemic attacks and stroke. Apolipoprotein E (ApoE) genotyping was performed on coded DNA samples, and participants were classified according to presence or absence of at least one ApoE-ε4 allele.

Statistical analyses

For all subjects, we calculated the duration of follow-up between start of the study and death, diagnosis of dementia or end of the study period, whichever came first. Prescription drug use was available on a day-to-day basis from the pharmacy prescription database. At each event date, we were therefore able to determine cholesterol-lowering drug use for the person who suffered the event and for all persons in the remainder of the cohort. Subsequently, cholesterol-lowering drug use was categorised as either "any" or "never" use, depending on whether a person had used cholesterol-lowering drugs prior to or on that event date, or not.[33] Hence, if, for a person, cholesterol-lowering drug therapy was initiated at some point during follow-up, that person would then switch from the exposure category of "never" use to "any" use. In case two prescriptions overlapped, the use of the first drug was assumed to have been discontinued and treatment to have proceeded with the second drug. A cohort member could contribute person-time to more than one category of cholesterol-lowering drug use if a person had used more than one cholesterol-lowering drug during follow-up. Accordingly, the numbers of cases in the analyses of the statin subtypes do not add up to the numbers of cases in the analyses of statins as a group. "Never" use of any cholesterol-lowering drug was the reference for all analyses. We distinguished between statin and non-statin cholesterol-lowering drugs and between lipophilic and hydrophilic statins. In addition, we separately investigated the use of simvastatin, the most lipophilic statin prescribed and pravastatin, the most hydrophilic statin prescribed.

We calculated the hazard ratio (HR and 95% CI) of the risk of AD associated with cholesterol-lowering drug use using a Cox proportional-hazards model with time-dependent covariates (SPSS 11.01 software). Calendar time was used as the time axis in the model to account for changes in prescription guidelines and availability of cholesterol-lowering drug use over time. All analyses were adjusted for age and sex, and, if applicable, use of other cholesterol lipid-lowering drugs (model I). To adjust for potential confounders, we additionally included baseline education, smoking, total serum cholesterol, body mass index, systolic blood pressure, and diabetes mellitus and cardiovascular disease. In addition, we included cardiovascular disease as a time-dependent covariate in the model to adjust for cardiovascular disease diagnosed during follow-up.

For statins, dose- and duration relationships were studied by dichotomising statin use around the median of the cumulative duration of use (⩽ and >2.9 years) and around the median of the defined daily dose (DDD), averaged over the total period of use used during follow-up (⩽ and >0.89 DDD).

We performed several additional subanalyses. First, we acknowledge that, even though cholesterol-lowering drug therapy is generally used chronically, persons could have stopped therapy, for example as a result of adverse events, non-compliance or a change in diet or lifestyle which rendered cholesterol-lowering therapy no longer indicated. To take this into account, we performed an analysis where we restricted the exposure category of "any" use to at least one prescription of cholesterol-lowering drugs filled in the year prior to the date of

Table 1 Baseline characteristics of the study population

Characteristic	(n = 6992)
Age (SD) in years	69.4 (9.1)
Sex (% female)	4195 (60.0%)
Smoking, ever (%)	4386 (62.7%)
Diabetes mellitus (%)	722 (10.3%)
Systolic blood pressure (SD) (mm Hg)	139.3 (22.3)
Cardiovascular disease (%)*	1877 (26.8%)
Cerebrovascular disease†	262 (3.7%)
Total cholesterol (SD) (mmol/l)	6.6 (1.2)
Body-mass index, mean (SD) (kg/m^2)	26.3 (3.7)
Primary education, low vocational training or less (%)	2697 (38.6%)
ApoE4 allele present (%)	1793 (25.6%)

*Myocardial infarction, coronary artery bypass graft, percutaneous transluminal coronary angioplasty, atrial fibrillation and heart failure.
†Stroke and transient ischaemic attack.
ApoE, apolipoprotein E.

an event. Second, most of the preceding cohort studies enrolled persons of 65 years and older in the early 1990s. Because statins were not widely used before the mid-1990s, it is likely that these persons did not use statins before the age of 65 contrary to our own study population. Therefore, we repeated the analysis for persons ⩾65 years of age at baseline. Third, we considered that physicians might be less motivated to prescribe chronic preventive therapies to persons with mild cognitive impairment. To evaluate whether this biased our results, we performed an analysis where we excluded the last 2 years before diagnosis. Fourth, in the main analyses, we used calendar time as time axis in the COX model. In an additional model, we used age as time axis, as was done in an earlier study on cholesterol-lowering drug use and AD.[8] By using age as time axis, no assumption is made on the functional form for the age-specific incidence rates. Finally, ApoE is responsible for lipid metabolism and is the primary transport protein of cholesterol in the brain.[34 35] Furthermore, it has been suggested that the response to statins is dependent on ApoE genotype.[9 36] Therefore, for statins we determined whether any effect modification was observed due to the presence of an ApoE4 allele.

RESULTS

In total, 6992 persons, free of dementia at baseline and with at least 6 months' medication history, were included in the analysis. In table 1, the baseline characteristics of the study population are given.

Persons were followed up to 15.3 years (average 9.2 years), with a total of 62 883 person years of follow-up. During follow-up, 739 persons developed dementia, of whom 582 were diagnosed as having AD, 81 with vascular dementia and 76 with other types of dementia. The total number of filled prescriptions during follow-up was 30 241. Prescription frequencies of statins and non-statin lipid-lowering drugs and for individual statins are shown in table 2. Simvastatin was the most frequently used statin, followed by pravastatin.

We observed that the use of statins was associated with a lower risk of AD than never use of cholesterol-lowering drugs. No protective effect was observed with the use of non-statin cholesterol-lowering drugs. Additional adjustment for other potential confounders did not change the estimates (table 3).

The effect sizes were equivalent for the use of lipophilic statins and hydrophilic statins versus never use (table 3). Compared with non-use, we did not find any evidence for a stronger protective effect for the lipophilic simvastatin than with the hydrophilic pravastatin (adjusted ORs: 0.61; 95% CI 0.36 to 1.03 and 0.38; 95% 0.15 to 0.99, respectively).

Table 2 Prescription frequencies of cholesterol-lowering drugs during follow-up

Cholesterol-lowering drug	Total no of filled prescriptions (% of total no of filled prescriptions, n = 30241)
Statins	27 713 (91.6%)
Lipophilic statins	21 855 (72.3%)
Simvastatin	17 742 (58.7%)
Atorvastatin	3949 (13.0%)
Cerivastatin	164 (0.5%)
Hydrophilic statins	5858 (19.4%)
Pravastatin	4079 (13.5%)
Fluvastatin	1735 (5.7%)
Rosuvastatin	44 (0.2%)
Non-statin cholesterol-lowering drugs*	2528 (8.4%)

*Fibrates, bile-acid binding resins or nicotinic acid and derivatives.

No dose–response relationship for statin use was detected, as dosages below and above the median were both associated with a decreased risk of AD (adjusted HR 0.57; 95% CI 0.32 to 1.00 for ⩽0.89 DDD and HR 0.58; 95% CI 0.32 to 1.04 for >0.89 DDD). Likewise, the protective effect was observed irrespective of duration of statin use (adjusted HR 0.44; 95% CI 0.25 to 0.80) for ⩽2.9 years and adjusted HR 0.78; 95% CI 0.44 to 1.32 for >2.9 years).

Our findings were robust in all planned subanalyses. Restricting the exposure definition of ''any use'' to at least one prescription in the year prior to the event date did not alter our findings: adjusted HR 0.51; 95% CI 0.31 to 0.83 for statin use and HR 1.55; 95% CI 0.54 to 4.44 for non-statin cholesterol-lowering drug use. Of the 30 persons who had used statins at time of Alzheimer diagnosis, 22 persons had filled at least one statin prescription in the year prior to diagnosis. For non-statin cholesterol-lowering drugs, this was five out of 12.

When we restricted our analyses to participants of 65 years and older at baseline, the HRs for AD remained similar (adjusted HR for statin use 0.61; 95% CI 0.38 to 0.98, adjusted HR for non-statin cholesterol-lowering drugs 1.14; 95% CI 0.49 to 2.68). The exclusion of 2 years before diagnosis did not change the magnitude of the estimates either. The adjusted HRs were 0.60 (95% CI 0.39 to 0.92) for statin use and 1.10 (95% CI 0.48 to 2.52) for non-statin cholesterol-lowering drug use versus never use. Likewise, if we used age as the time axis rather than calendar time, the associations remained unchanged (adjusted HR for statin use 0.55; 95% CI 0.36 to 0.86, adjusted HR for non-statin cholesterol-lowering drugs 1.17; 95% CI 0.52 to 2.64). Finally, in the analyses where we stratified on the presence or absence of an ApoE4 allele, the protective effect of statin use was similar for persons with an ApoE4 allele (adjusted HR 0.50; 95% CI 0.26 to 0.94) and for persons without an ApoE4 allele (adjusted HR 0.61; 95% CI 0.32 to 1.18).

DISCUSSION

In the prospective population-based cohort of the Rotterdam Study, we found that the use of statins, but not of non-statin cholesterol-lowering drugs, was associated with a lower risk of AD compared with never use of cholesterol-lowering drugs. No difference was observed between the effects of hydrophilic and lipophilic statins.

Strengths of our study include the active surveillance of incident dementia, including in-person screening, together with the high response rate and virtually complete follow-up, which

Table 3 Hazard ratios (HR) of Alzheimer disease with the use of statins, lipophilic and hydrophilic statins separately, and non-statin cholesterol-lowering drugs

	Alzheimer disease			
Exposure	Cases	HR (95% CI) Model 1*	Cases	HR (95% CI) Model 2†
Never use	546	1.00 (ref.)	438	1.00 (ref.)
Statins‡	30	0.58 (0.38 to 0.88)	28	0.57 (0.37 to 0.90)
Lipophilic statins	25	0.55 (0.34 to 0.89)	23	0.54 (0.32 to 0.89)
Hydrophilic statins	9	0.52 (0.26 to 1.05)	9	0.54 (0.26 to 1.11)
Non-statin cholesterol-lowering drugs§	12	1.04 (0.45 to 2.40)	12	1.05 (0.45 to 2.44)

*Model 1: age, sex-adjusted and use of other lipid-lowering drugs, if applicable.
†Model 2: as Model 1 additionally adjusted education, systolic blood pressure, smoking, total serum cholesterol, body mass index, diabetes mellitus and cardiovascular and cerebrovascular disease.
‡The number of exposed cases for any statin differs from the sum of exposed cases for statin subtypes. This is because persons can contribute exposed person-time to more than one type of statin.
§Fibrates, bile-acid-binding resins or nicotinic acid and derivatives.

limited the chances of selection or information bias. An important asset of our study is the availability of continuous pharmacy dispensing data on all members of the cohort. In terms of exposure misclassification, this constitutes a major advantage compared with studies that have to rely on self-reported drug use and drug exposure obtained at baseline.[11 12] Nevertheless, contrary to a clinical trial setting, treatment was not randomly assigned in our study, and confounding by indication should be considered. In the case of lipid-lowering drugs, physicians might less readily prescribe these agents to individuals with early signs of cognitive impairment because of concerns regarding adherence, treatment complications and priorities in healthcare resource allocation. However, the results did not change when we included a 2-year lag-period before diagnosis of AD, which suggested that this confounding by indication did not play a major role, if any, in our study. Finally, the number of exposed cases available in the analyses limited extensive analyses of duration of use and in various patient groups.

We found that statin use was associated with a reduced risk of AD. Our findings are in line with the cross-sectional reports, which showed a lower prevalence of dementia among statin users.[1–3] Most of the prospective studies did not find a protective effect of statins or only for persons younger than 80 years of age.[3 7–10 12 13] Important limitations of these studies included the limited durations of follow-up, as short as 3 years,[12] and low number of incident Alzheimer cases.[11 12] Moreover, several studies relied, in part, on (self) reported drug use at baseline, with persons who started statin therapy during follow-up consequently being classified as non-users.[3 11 12] This may have led to misclassification of drug exposure and, hence, may have biased the risk estimates towards one. In the very large population database of the United States Veterans Affairs (VA) medical system, a protective effect was specifically observed with the use of simvastatin, but not for other statins.[37] The latter study is different from previous observational studies in that persons taken cardiovascular medication, excluding statins, were used as the comparator group. In our analyses, adjustment for cardiovascular disease did not change the observed associations. Some clinical studies have studied the effect of statins on cognitive decline, but thus far none have reported on the prevention of AD with statins or other lipid-lowering drugs.[14–16] We did not find a duration–response relationship. Only a few other observational studies investigating the use of statins and incident AD report on the duration of statin use. Zamrini *et al*[7] reported a weakened protective effect among those with 12 months of more use, while a post-hoc analysis by Zandi *et al*[12] observed a reduced risk for AD with more than 3 years of statin use. Further research would be required to investigate these aspects of statin use.

In our study, both hydrophilic and lipophilic statins were associated with a reduced risk of AD. Two other prospective studies specifically investigated lipophilic and hydrophilic statins separately but found neither associated with a reduced risk of AD.[10 13] As mentioned above, results from the VA database showed a protective effect for the lipophilic simvastatin but not for other statins.[37] Our observation of a protective effect regardless of the lipophilicity of statins challenges the hypothesis that only lipophilic statins would reduce the risk of AD. Various explanations could be given as to why no difference in effect for lipophilic and hydrophilic statins was observed. One, though many studies show that the ability of statins to permeate the blood–brain barrier depends on their lipophilic or hydrophilic character,[23 24 26] many other factors besides lipid solubility also determine a drug's distribution in different tissues. These include pharmacokinetic properties and the affinity to specialised transport mechanisms.[20 21 23 24] For example, although atorvastatin is lipophilic by nature, it is suggested that little of the drug is distributed beyond the liver, as had been expected.[22] Two, if changes in endogenous cholesterol synthesis cause alterations of brain cholesterol metabolism, the ability of statins to cross the blood–brain barrier might be irrelevant. This would also hold if statins act through a mechanism for which brain penetration might not be important at all. Besides inhibition of cholesterol synthesis, statins namely also affect physiological processes such as endothelial functioning, atherosclerosis and oxidative stress reactions.[38] Many of these processes have also been associated with AD. Other effects, more typical of Alzheimer pathology, could include inhibition of amyloid synthesis and reduction of neurofibrillar tangle burden.[13 39] At least for some of these mechanisms, it is likely that brain penetration of statins is extraneous.

The effect of statins on Alzheimer risk was not modified by the ApoE4 genotype. ApoE is essential in cholesterol metabolism, and it is suggested that the response to statin treatment varies with ApoE genotype, though agreement in the literature is not complete.[36] Our results comply with two other observational studies that did not find evidence for effect modification by the ApoE4 genotype.[6 12] A recent report by Li *et al* found a lower risk of AD with statin use for persons with at least one ApoE4 allele.[9] Further investigations will be needed to provide conclusive results regarding a possible effect modification by ApoE genotype.

In conclusion, the use of statins is associated with a decreased risk of AD independent of their relatively lipophilicity.

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