Articles

Statins and the risk of dementia

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Summary

Background Dementia affects an estimated 10% of the population older than 65 years. Because vascular and lipid-related mechanisms are thought to have a role in the pathogenesis of Alzheimer's disease and vascular dementia, we did an epidemiological study of the potential effect of HMGCoA (3 hydroxy-3methylglutaryl-coenzyme A) reductase inhibitors (statins) and other lipid-lowering agents on dementia.

Methods We used a nested case-control design with information derived from 368 practices which contribute to the UK-based General Practice Research Database. The base study population included three groups of patients age 50 years and older: all individuals who had received lipid-lowering agents (LLAs); all individuals with a clinical diagnosis of untreated hyperlipidaemia; and a randomly selected group of other individuals. From this base population, all cases with a computer-recorded clinical diagnosis of dementia were identified. Each case was matched with up to four controls derived from the base population on age, sex, practice, and index date of case.

Findings The study encompassed 284 cases with dementia and 1 080 controls. Among controls 13% had untreated hyperlipidaemia, 11% were prescribed statins, 7% other LLAs, and 69% had no hyperlipidaemia or LLA exposure. The relative risk estimates of dementia adjusted for age, sex, history of coronary-artery disease, hypertension, coronary-bypass surgery and cerebral ischaemia, smoking and body mass index for individuals with untreated hyperlipidaemia (odds ratio 0·72 [95% CI 0·45–1·14]), or treated with non-statin LLAs (0.96 [0·47–1·97], was close to 1·0 and not significant compared with people who had no diagnosis of hyperlipidaemia or exposure to other lipid-lowering drugs. The adjusted relative risk for those prescribed statins was 0·29 (0·13–0·63; p=0·002).

Interpretation Individuals of 50 years and older who were prescribed statins had a substantially lowered risk of developing dementia, independent of the presence or absence of untreated hyperlipidaemia, or exposure to non-statin LLAs. The available data do not distinguish between Alzheimer's disease and other forms of dementia.

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Introduction

Cognitive impairment in elderly people, once called senile dementia, is now known to be a heterogeneous condition that in most cases has pathological features consistent with Alzheimer's disease.[1] Other less common causes of cognitive impairment include vascular dementia whose definition and distinction remain controversial;[2,3] mixed dementia, with features of both Alzheimer's disease and vascular dementia; frontotemporal dementia,[4] Lewy body dementia,[5] and others.[6] Although a small number of early onset, dominantly inherited cases of familial Alzheimer's disease[7] and frontotemporal dementia[8] are caused by genetic mutations, the cause of most sporadic cases of dementia is presently unknown.

There is evidence to suggest a relation between lipids and vascular changes involving the brain in dementia. These associations include: recognition that the ε4 apolipoprotein allele (APOEε4) is a risk factor for Alzheimer's disease;[9] epidemiological studies linking vascular risk factors to dementia;[10] awareness that very small strokes can precipitate clinical dementia in cognitively normal elderly people with Alzheimer's disease pathology;[11] the effect in cell culture of cholesterol on degradation of the amyloid precursor protein;[12] the abnormal appearance of microvascular endothelial cells in affected brain areas in Alzheimer's disease;[13] and a possible role of the LDL receptor-related protein in Alzheimer's disease.[14] The precise mechanisms by which any or all of these lipid and vascular factors might be associated with dementia in elderly individuals are at present poorly understood.

We decided to explore the possibility that modifying patients' lipid burdens or components, or improving their microvascular endothelial function, or both, could lower the risk of developing dementia. Since practical considerations would preclude undertaking a therapeutic trial for the prevention of dementia, we chose to examine this hypothesis by using an observational epidemiological approach. Lipid-lowering agents (LLAs), particularly HMGCoA-reductase inhibitors (statins), seem to be beneficial in protecting against certain arterial disorders. Since dementia may at least in part to be associated with vascular disorders,[15] we carried out an observational study of lipid-lowering agents and dementia based on the General Practice Research Database.

Methods

Study population and data source

The General Practice Research Database has been previously described in detail elsewhere.[16,17] Since 1987, more than 3 million residents in the UK have been enrolled with selected general practitioners who have agreed to provide data for research purposes to the database. The information recorded includes patient demographics and characteristics (eg, height, weight, smoking status), symptoms, medical diagnoses, referrals to consultants, hospital admissions, and drug

Characteristics	Cases (n=284)	Controls (n=1080)	Relative risk estimate (95% CI)
Age (years)			
50–59	7 (2%)	29 (3%)	..*
60–69	30 (11%)	131 (12%)	..
70–79	108 (38%)	407 (38%)	..
80–89	139 (49%)	513 (47%)	..
Sex			
Male	113 (40%)	421 (39%)	..*
Female	171 (60%)	659 (61%)	..
Body mass index (kg/m²)			
⩾28	32 (11%)	214 (20%)	1·00
23–27·9	72 (25%)	333 (31%)	1·45 (0·91–2·32)
<28	48 (17%)	121 (11%)	2·69 (1·57–4·61)†
Unknown	132 (47%)	412 (38%)	2·32 (1·39–3·86)
Smoking status			
Non-smoker	145 (51%)	647 (60%)	1·00
Current	41 (15%)	85 (8%)	1·90 (1·21–2·96)‡
Ex-smoker	23 (8%)	106 (10%)	0·94 (0·56–1·57)
Unknown	75 (26%)	242 (22%)	1·16 (0·78–1·73)
Coronary-artery disease	67 (24%)	320 (30%)	0·82 (0·58–1·16)†
Diabetes mellitus	30 (11%)	103 (10%)	1·32 (0·84–2·06)
Transcient cerebral ischaemia	34 (12%)	97 (9%)	1·37 (0·88–2·12)
Hypertension	80 (28%)	385 (36%)	0·86 (0·62–1·17)
Coronary-artery bypass surgery	9 (3%)	26 (2%)	2·95 (1·13–7·68)
Oestrogen use	2 (0·7%)	8 (0·7%)	1·02 (0·16–6·59)

Values shown as mean (SD). *Matching variables, therefore no relative risk estimate calculated. †p<0·001, ‡p=0·005, §p=0·03.

Table 1: **Characteristics of participants and their multivariate effects on risk of dementia**

prescriptions (including the specific preparation, route of administration, dose, and number of tablets for each prescription). On request, hospital discharge and referral letters are available for review to validate the diagnoses recorded in the computer record. The database has been the source for numerous epidemiological studies in recent years, and the accuracy and completeness of these data have been well documented and validated.[16,17] All of the information received by investigators is anonymised.

Base population and follow-up

Within the database, a study population consisting of three separate groups was identified. Group I included all patients aged 50–89 years with at least one prescription for a statin at any time (ie, atorvastatin, cerivastatin, fluvastatin, pravastatin, or simvastatin) or an LLA other than statins (ie, bezafibrate, ciprofibrate, clofibrate, fenofibrate, gemfibrozil, colestipol, cholestyramine, acipimox, or niacin/nicotinic acid). Group II included patients with a computer-recorded International Classification of Diseases coded diagnosis of hyperlipidaemia who did not receive any lipid-lowering drug treatment. Group III was a random sample of 25 000 people between the age of 50–89 years who had neither a computer-recorded diagnosis of hyperlipidaemia nor a prescription for a lipid-lowering drug at any time. Within this base population consisting of the three groups, we followed each participant from Jan 1, 1992, to Jan 1, 1998.

We excluded people with a computer-recorded diagnosis of alcoholism or drug abuse, cancer (but not with non-melanoma skin cancer), multiple sclerosis, chronic psychosis, motor neuron disease, Parkinsonism, Down's syndrome, chronic liver disease, chronic renal disease, epilepsy, and stroke at any time before the date of diagnosis of dementia.

Case definition and nested case-control analysis

Within the base population (ie, the three study groups combined) we identified all participants who developed a first-time diagnosis of dementia or Alzheimer's disease. In a previous study on oestrogen replacement therapy and dementia[18] we reviewed 80 case records of people with these diagnoses. 90% of the people recorded as having dementia or Alzheimer's disease, on detailed review of the records by two of us (DD, SS), without knowledge of drug exposure, were thought to have well-documented progressive dementia. Of those with a diagnosis of Alzheimer's disease, for whom adequate data were available, 84% were judged to have clinical evidence of possible or probable Alzheimer's disease, using NINCDS-ADRDA criteria.[19] We assume that the diagnostic accuracy is similar among the population in the present study. In the current study, the date of the first diagnosis of dementia is subsequently referred to as the index date. Some of the cases had statins started after the diagnosis of dementia was made. These participants were thought to be not exposed to statins since the use of statins started after the diagnosis of Alzheimer's disease.

From the study base population, we randomly selected up to four controls—ie, people without a diagnosis of dementia, matched to each individual with dementia by age (SD 1 year), sex, calendar time (by using the same index date as for cases), practice, and years of previous recorded history in the database (matching on number of years of medical and drug history before the index date). Controls had to be alive at the index date. The same exclusion criteria were applied to controls.

Exposure	Cases	Controls	Adjusted relative risk estimate (95% CI)	p value
None, normal lipids	218 (76·8)	746 (69·1)	1·0	..
Hyperlipidaemia alone (no drug treatment)	29 (10·2)	142 (13·2)	0·72 (0·45–1·14)	0·16
Current use of statins	12 (4·2)	100(9·3)	0·29 (0·13–0·63)	..
Current use of statins and other LLA	1 (0·4)	4 (0·4)	..	..
Past use of statins	0 (0·0)	14 (1·3)	..	..
Current use of other LLA	11 (3·9)	42 (3·9)	0·96 (0·47–1·97)	0·91
Past use of other LLA	13 (4·6)	32 (3·0)	1·31 (0·66–2·61)	0·44

*Adjusted for body mass index, smoking, hypertension, previous history of coronary-artery disease, coronary-artery bypass surgery, diabetes mellitus, and transient cerebral ischaemia.

Table 2: **Adjusted risk ratio estimates for various exposures compared with non-exposed and hyperlipidaemia**

Exposure	Cases (n=284)	Controls (n=1080)
None	247	888
Type of statin*		
Simvastatin	9	78
Pravastatin	3	23
Atorvastatin	1	10
Fluvastatin	0	5
Cerivastatin	0	2
Duration of use on statins		
<2 years	6	83
2–4 years	5	21
⩾4 years	2	14
Duration of use of non-statin LLAs		
<2 years	12	45
2–4 years	7	18
⩾4 years	5	11

*Includes one case and four controls who received another LLA in addition to a statin. All data are number of participants.

Table 3: **Distribution of statin users in participants by duration of use and type of statin**

Statistical analysis

We did a matched analysis (conditional logistic regression) to explore the association between the risk of dementia according to type of drug exposure (statins or other LLAs) and untreated hyperlipidaemia. Individuals exposed to none of these were used as the reference group for estimates of relative risk. Current use of an LLA was defined as receipt of at least one prescription within 180 days preceding the index date. All other recipients of LLAs were judged to be past users.

In addition to controlling for age, sex, calendar time, practice, and years of recorded history in the database before the index date by matching, we controlled for smoking, body mass index, previous history of coronary-artery disease, previous coronary-bypass surgery, transient ischaemic attacks or cerebral vascular insufficiency, hypertension, and diabetes. We used SAS (version 6.12) to analyse the data.

Results

The base population consisted of 24 480 individuals who were users of LLAs (group I), 11 421 people with a diagnosis of hyperlipidaemia who did not use LLAs (group II), and 25 000 who did not receive LLAs and did not have a recorded diagnosis of hyperlipidaemia.

We identified 284 eligible cases who had a first-time diagnosis of dementia and 1080 matched controls. Of the controls, there were 746 (69%) without hyperlipidaemia or LLA drug treatment, 142 (13%) with hyperlipidaemia who received no drug treatment, 114 (11%) who had received statins, 74 (7%) who had received other non-statin LLAs, and four who had received statins and other LLAs (0.4%; table 1). The average number of years of medical history recorded before the index date was similar for cases and controls (5.53 and 5.51 years, respectively). Table 1 shows the baseline characteristics of the particpants. These covariates were adjusted for in all subsequent multivariate analyses. The relative risk estimate (odds ratio) for individuals with dementia and with untreated hyperlipidaemia was 0·72 (0·45–1·14); the relative risk estimate for current statin users was 0·29 (0·13–0·63); p=0·002); whereas for recipients of other LLAs the relative risk was 0·96 (0·47–1·97), as shown in table 2. There were only 14 past users of statins, none of whom had dementia; among the past users of other LLAs the relative risk of dementia was 1·31 (0·66–2·61).

Since there were only 13 cases of dementia among patients exposed to statins we did not think that is would be informative to explore further the effect of duration of use of individual statins in a formal analysis. The distribution of the duration of use in cases compared with controls is provided in table 3.

We further stratified the analysis of current use of statins or other LLAs by age and sex to detect possible effect modification. The results of these analyses did not suggest that the effect of statins on dementia risk differed materially by age or sex. The effects of exposure to individual statins on the risk of developing dementia was similar for all individual statins (table 3). Risk factors that were independently associated with an increased risk of dementia in the multivariate analysis were a history of coronary-artery bypass surgery (adjusted relative risk 2.97 [95% CI 1·13–7·68]), smoking (1.90 [1·21–2·96]), and the lowest body mass index subgroup compared with the highest category (2.69 [1·57–4·61). The mean time intervals for body mass index measurement preceding the index date were similar for cases and controls (2·24 years and 2·64 years, respectively).

Discussion

We have shown that people in the UK who are prescribed statins have a risk of dementia, clinically diagnosed by general practitioners and their consultants, which to our best estimate is 70% lower (but at least 37% lower) than those who do not have hyperlipidaemia or who are not on LLA treatment. This is not due to the indication for statin use—namely hyperlipidaemia—since people with this diagnosis who did not receive LLAs had no significant reduction in risk for dementia. It is also not due to the indication for prescribing LLAs per se since people with hyperlipidaemia prescribed non-statin LLAs did not have a reduced risk for dementia. The possibility that the reduced risk with statins was because of the shorter period of observation for the development of dementia was also precisely controlled for in the analyses, and patients who had received non-statin LLAs for similar time periods to those individuals treated with statins had no reduction in risk. Furthermore, the reduction in risk for dementia was not due to other risk factors controlled for in the analyses (table 2). Nevertheless, it is possible that patients who received statins were selected with regard to level of education, socioeconomic status, and cholesterol, which themselves may be linked to the risk of dementia. Information on these variables was not available.

In our previous study,[18] most (90%) patients diagnosed with either dementia or Alzheimer's disease by the database practitioners were found on detailed analysis to have progressive dementia. Most practitioners made the diagnosis when dementia was moderately advanced and unequivocal. Of those diagnosed by the database practitioners as having Alzheimer's disease, 84% were classified as having possible or probable Alzheimer's disease on review. In the current study, by matching cases and controls from the same practice, the effect of variations in the clinical acumen of individual practitioners and their diagnostic threshold for dementia is lower. Non-differential misclassification of dementia, if present, would tend to diminish the ability to detect a protective effect of statins.

Since the quality and completeness of the drug exposure and outcome data which form the basis of our study are well documented, there are two possible explanations other than chance for the finding of a reduced risk of dementia related to statins. First, the reduced risk could be caused by some other characteristics of the statin recipients, that are not measured in this study, which themselves are associated with a lowered risk of dementia. Second, the statins themselves reduce the risk of dementia.

It is commonly said that observational epidemiological studies do not prove causality and therefore need not be taken seriously.[20] Less commonly pointed out is that observational studies usually describe causal links. Many examples of observational studies presenting evidence for a causal association may be cited. A strong negative association between aspirin and myocardial infarction was reported in 1974,[21] a strong negative association between folic acid intake in the first trimester of pregnancy and neural tube defects was reported in 1989,[22] and five observational studies reported an increased risk for venous thromboembolism among oestrogen users. All of these epidemiological findings have been substantiated in clinical trials.

Nevertheless, many observational studies provide results which are not causal. Indeed, they may be spurious. The explanation for such findings is regularly due to problems with epidemiological technique.[23] In

studying the effects of oestrogen in Alzheimer's disease, for example, a number of studies have yielded conflicting results.[18] In many published studies, information regarding exposure to the study drugs was incomplete, the dates and duration of exposure to study drugs in relation to the onset of dementia was uncertain, and potential confounding factors were inadequately controlled making the results ambiguous.

In our study, although many confounders were controlled for, and the data-specific information regarding the use of LLAs was highly accurate, we appreciate that data regarding two aspects of the study were accepted without detailed record review: the practitioners' diagnoses of dementia, and of hyperlipidaemia. We also did not separately analyse individuals with hyperlipidaemia by lipid profiles, or by individual responses to LLAs. Although these data would be interesting and informative, inconsistency in either of these data would increase the statistical noise and decrease the ability of this study to recognise any real drug effect on the risk of dementia.

The validity and interpretation of the results, and conclusions of drug-related epidemiological studies is dependent on the quality of the study design as well as the completeness of the crucial data elements which are used to derive the results and draw inferences.[23] Each reader must make an informed judgement on this matter.

From our study it is not possible to find out the mechanisms by which statins might reduce the risk of developing dementia. The evidence from this study, and from previous experimental and clinical studies of statin functions and mechanisms of dementia, provide a basis for further consideration. Statins are known to competitively inhibit the synthesis of cholesterol, preventing the conversion of HMGCoA to mevalonate. They reduce the formation and entry of LDL cholesterol into the circulation, and upregulate LDL receptor activity; serum LDL cholesterol and triglycerides are reduced, and HDL cholesterol is increased.[24] In our study, the observations that statins reduced risk of dementia, whereas other LLA, normal lipid concentrations, or hyperlipidaemia, did not suggest that LDL cholesterol levels themselves were not central to the effect of statins. Other studies have also failed to show a difference in risk of dementia or Alzheimer's disease based on current cholesterol concentrations.[25,26] Similarly, our finding is similar to the observation in other conditions, such as myocardial infarction (MI) or stroke, that statins appear to improve prognosis, both for further vascular disease (MI, stroke) and for survival, beyond a measured effect on cholesterol concentrations.[27]

Statins also have beneficial effects on the microvasculature, including increasing endothelial nitric oxide synthase (eNOS)[27,28] and reducing endothelin-1,[29] thereby dilating capillaries and increasing blood flow. In Alzheimer's disease cerebral perfusion is decreased in affected areas of brain,[30] capillary endothelium shows pathologic changes,[13] and eNOS is decreased in capillaries in the brains.[31,32] The effect of statins in reducing the risk for dementia may involve such beneficial effects on the cerebral capillary endothelium, or other properties of the drugs.

An important question is whether the statins' apparent reduction in risk for dementia may also be present for dementing disorders. The data available in this study do not answer this question. In Western countries, however, Alzheimer's disease causes a considerable majority of cases of dementia,[33] as is the case for the population used in this study, although not all cases were specifically diagnosed as having Alzheimer's disease. To address this issue, we determined the relative risk estimates for dementia among statin-treated individuals with and without adjustment for certain vascular risk factors, and found no difference in the effect. We determined the relative risk for dementia in the group diagnosed as "dementia" as compared with those diagnosed as "Alzheimer's disease", and found no material difference in effect. This suggests that there may be a common risk factor for dementia related to the effect of statins.

If substantiated, the implications of this observational study are considerable. These findings suggests that the use of statins could substantially reduce the risk of dementia in the elderly, either by delaying its onset, or by opposing specific or general age-related changes that result in cognitive impairment. We are aware of the substantial potential consequences of this publication, and that our data should be replicated by additional studies (another study on the subject has been published[34]). Given the potential impact of this study, additional studies of acceptable quality are urgently needed.

Contributors

H Jick designed the study, reviewed the data, interpreted the results, and wrote the paper. D A Drachman initiated the study and provided the background data for the study. S S Jick reviewed the data and wrote the paper. S Seshadri provided the background data for the study. G L Zornberg initiated and designed the study, did the statistical analyses, interpreted the results, and wrote the paper.

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