I, Kimberley Severin, hereby submit this original work as part of the requirements for the degree of Master of Science in Epidemiology (Environmental Health).

It is entitled:
Statins and Risk of Alzheimer Disease: A Systematic Review and Meta-Analysis

Student’s name: Kimberley Severin

This work and its defense approved by:

Committee chair: Kim Dietrich, PhD

Committee member: Paul Succop, PhD

Committee member: Jeffrey Welge, PhD
Statins and Risk of Alzheimer Disease: A Systematic Review and Meta-Analysis

A thesis submitted to the
Graduate School
of the University of Cincinnati
in partial fulfillment of the
requirements for the degree of

Master of Science

in the Department of Environmental Health
of the College of Medicine
by

Kimberley Severin

Bachelor of Science, Chemical Engineering

University of Cincinnati, June 1992

Committee Chair: Kim Dietrich, Ph.D.
ABSTRACT

Objective: The objective of this research was to assess the effects of statins in the prevention of Alzheimer disease.

Methods: A systematic review of MEDLINE (PubMed) was performed to identify all available published prospective studies that evaluated the effect of statin treatment on the incidence of Alzheimer disease in individuals with normal cognitive function at baseline. After the relevant studies were identified, a meta-analysis was conducted. A random-effects model was applied to compute the weighted estimate of the average treatment effect of statins on the risk of incident Alzheimer disease.

Results: Six prospective cohort studies with a total of 20,591 participants met the pre-specified selection criteria for inclusion in the meta-analysis. The mean age of participants was ≥65 years across the six studies. Participants were followed from 3 to 17 years. From the random-effects model, the hazard ratio for Alzheimer disease in statin users as compared with nonusers was 0.76 (95% confidence interval, 0.55 to 1.06).

Conclusions: The random-effects model predicted that statin use is associated with an average reduction in risk of Alzheimer disease of 24%. Although the 95% confidence interval included the null value of 1.0, the non-significant result may be due to reduced statistical power. Additional research is recommended to define the patient populations for whom statin therapy is beneficial and the appropriate type, dose, and duration of statin treatment.
ACKNOWLEDGMENT

This thesis is based on an independent research project. The author planned the research and performed the data collection and statistical analysis. The author thanks the members of the thesis committee – Kim Dietrich, Ph.D., Jeffrey Welge, Ph.D., and Paul Succop, Ph.D. – for their thoughtful critique of the research paper and their comments on considerations for interpretation and implications of the results.
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INTRODUCTION

Alzheimer disease is a neurodegenerative disorder characterized by cognitive and memory deterioration, progressive impairment of activities of daily living, and behavioral and psychological disturbances. The pathophysiology of Alzheimer disease involves the deposition of extracellular plaques containing beta-amyloid peptide and the accumulation of intracellular neurofibrillary tangles of tau protein. It is hypothesized that the end result of the amyloid cascade of events is widespread loss of neurons and their synapses, causing memory decline and dementia.\(^1\)

Alzheimer disease has become a public health issue of increasing importance as a result of aging of the population. The Alzheimer’s Association estimates that more than 5 million Americans have Alzheimer disease.\(^2\) By 2050, the number of individuals 65 years of age and older with Alzheimer disease could range from 11 to 16 million. For people with Alzheimer disease and other dementias, aggregate payments for health care, long-term care, and hospice are projected to increase from $183 billion in 2011 to $1.1 trillion in 2050. The burden of caring for patients has a negative impact on the health, employment, and financial security of many caregivers. Current treatments are primarily symptomatic, in that they provide temporary cognitive improvement without slowing disease progression. Therefore, there is an unmet need for new and more effective treatments and prevention strategies.

Increasing evidence indicates a link between cholesterol and Alzheimer disease. Cholesterol may be involved in the metabolism of beta-amyloid, although this process is not fully understood. Animal studies have found that dietary cholesterol increases beta-amyloid deposits in the hippocampus.\(^3,4\) In mouse models, statin treatment decreases blood cholesterol levels and amyloid deposition.\(^5\) Neuropathological studies in humans indicate a strong linear
association between increased low-density lipoprotein cholesterol levels and increased numbers of senile plaque or neurofibrillary tangles.  

Long-term population studies have shown that elevated cholesterol levels in mid-life are associated with a higher risk of Alzheimer disease in later life. This association between hypercholesterolemia and Alzheimer disease risk offers a rationale for the use of lipid-lowering medications to protect against Alzheimer disease. Statins, a class of drugs widely used for the treatment of hypercholesterolemia, have demonstrated some apparent promise as potential preventive agents for Alzheimer disease. Several observational studies have reported a lower occurrence of dementia and Alzheimer disease among users of statins and other lipid-lowering medications. 

An autopsy study demonstrated that the brains of statin users exhibited a lower burden of Alzheimer disease pathology when compared with nonusers. Clinical trials have shown that lovastatin and simvastatin modulate the processing of the amyloid precursor protein and resulting beta-amyloid production. Simvastatin treatment in hypercholesterolemic patients significantly reduced circulating levels of 24S-hydroxycholesterol (cerebrosterol), providing evidence that simvastatin affects cholesterol metabolism in the human brain. Due to the multifactorial actions of statins, it is biologically plausible that statins may reduce risk of dementia and Alzheimer disease, independently of their effects on serum cholesterol. Other proposed mechanisms specific to statins include their anti-inflammatory and vascular effects and altered expression of genes related to cell growth, signaling, trafficking, and apoptosis.

The objective of this research was to conduct a systematic review and meta-analysis of prospective studies to assess the effects of statins in the prevention of Alzheimer disease. The central hypothesis was that statin treatment significantly reduces the risk of Alzheimer disease.
METHODS

Literature Search

A systematic review of MEDLINE (PubMed) was performed to identify all available prospective studies published as of March 2012 that evaluated the effect of statin treatment on the incidence of Alzheimer disease. Search terms included statin, lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin, or rosuvastatin in combination with Alzheimer disease, dementia, or cognitive impairment. Study selection criteria included the following: 1) original prospective epidemiologic study or randomized controlled intervention trial that compared statin users/statin-treated subjects with nonusers/placebo-treated subjects; 2) assessment of incident Alzheimer disease as primary or secondary outcome parameter using standard diagnostic criteria in population with normal cognitive function at baseline; and 3) post-baseline follow-up time of at least 1 year as this was considered the minimum amount of time to convert to diagnosed Alzheimer disease from a cognitively normal status at baseline and allow for an adequate evaluation of the effect of statins on the risk of Alzheimer disease.

Review articles were excluded but scanned to determine that no eligible study was missed by the literature search. Only studies with results available in the English language were included; this did not lead to the exclusion of any studies.

Study design, characteristics of exposure, incident case ascertainment, number of cases, and measures of relative risk and their corresponding 95% confidence intervals (CIs) were recorded.

Statistical Analysis

After the relevant studies were identified, a meta-analysis was conducted. The primary outcome was the relative risk of diagnosed Alzheimer disease for statin users as compared with
nonusers. A random-effects model was applied to compute a weighted estimate of the average treatment effect on the primary outcome measure and its corresponding 95% CI as this model accounts for between-studies heterogeneity. For studies that reported the relative risk from both crude (unadjusted) and adjusted analyses, the relative risk estimate from the fully adjusted model including all potential confounders was used in the analysis. The logarithm of the adjusted relative risk with its corresponding standard error was extracted from the reported estimate and its 95% CI for each study.

Random-effects models were planned to be used to calculate average effect sizes on changes in scores from standardized tests of cognitive function if available.

Comprehensive Meta-Analysis (Version 2.0) software was used for the statistical analysis.

RESULTS

Search Results

Figure 1 shows the flow diagram of the study selection process. The literature search returned 272 publications. After review of titles and abstracts, 20 were considered as potentially eligible and the full-text publications were screened. Fourteen of the 20 studies were excluded for the following reasons: 11 studies did not have a validated diagnosis of Alzheimer disease as an outcome measure; 1 study was not prospectively designed; 1 study population was not cognitively normal at baseline; and 1 was a duplicate publication with no additional information or data. Six studies met the pre-specified eligibility criteria for inclusion in the meta-analysis.22-27
Description of the Included Studies

Table 1 summarizes the design and results of the individual studies. Five were prospective cohort studies (18,358 participants),\textsuperscript{22,23,25-27} and one was a secondary analysis of a clinical trial cohort (2233 participants).\textsuperscript{24} All studies drew samples from the community, five in the United States and one in The Netherlands. In all six studies, the mean age of participants was \( \geq 65 \) years. Participants were followed from 3 to 17 years. All studies used proportional hazards regression models to compute hazard ratios (HRs). In adjusted analyses, three studies reported a significant reduction in risk of Alzheimer disease with statin use.\textsuperscript{22-24} Three studies did not find a significant association between statin use and risk of incident Alzheimer disease.\textsuperscript{25-27}

Participants in the six studies were cognitively normal at baseline, as assessed by cognitive screening tests such as the Mini Mental State Examination, and underwent standardized dementia diagnostic evaluations from expert physicians at annual intervals. Dementia evaluations followed a protocol that included a detailed history from participants and informants and physical, neurologic, and neuropsychological examinations. Clinical evaluations in the Religious Orders Study, in particular, followed procedures recommended by the Consortium to Establish a Registry for Alzheimer’s Disease (CERAD).\textsuperscript{28,29} Relevant laboratory tests and neuroimaging tests were performed for differential diagnosis. In all six studies, a panel of clinicians diagnosed probable Alzheimer disease using the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA) Alzheimer’s criteria.\textsuperscript{30} The NINCDS-ADRDA criteria require that the presence of cognitive impairment and a suspected dementia syndrome be confirmed by neuropsychological testing for a clinical diagnosis of possible or probable Alzheimer disease. Histopathologic confirmation is required for the definitive diagnosis.
The Adult Changes in Thought study was a community-based prospective cohort study with participants ≥65 years of age from members of a Seattle health maintenance organization. Participants were enrolled in the original cohort from 1994 to 1996, and in the expansion cohort from 2000 to 2002. Ongoing statin use for the exposed group was documented by pharmacy records. Over an average of 6 years of follow-up of 3099 participants, 263 participants developed Alzheimer disease. The adjusted HR for Alzheimer disease with statin use was 0.62 (95% CI, 0.40 to 0.97) in a model that included demographic characteristics and vascular risk factors as covariates. The strength of the association decreased with age.

The Rotterdam Study was a prospective, population-based cohort study of age-related disorders conducted in The Netherlands. A total of 6992 participants ≥55 years of age (mean 69 years) were followed from baseline (1990–1993) until 2005 for incident Alzheimer disease. Exposure was use of any statin during the study documented by pharmacy records. During follow-up (mean 9 years), 466 persons developed Alzheimer disease. Compared with never use of cholesterol-lowering drugs, statin use was associated with a decreased risk of Alzheimer disease (adjusted HR, 0.57; 95% CI, 0.37 to 0.90) in a model that adjusted for demographic characteristics and vascular risk factors. No protective effect was observed with the use of non-statin cholesterol-lowering drugs.

Sparks et al. reported the observational results of elective statin use in a randomized, double-blind, placebo-controlled clinical trial of two anti-inflammatory medications for the primary prevention of Alzheimer disease in an at-risk population of elderly individuals (Alzheimer’s Disease Anti-inflammatory Prevention Trial [ADAPT]). Eligible participants were ≥70 years of age and had a history of at least one first-degree relative with Alzheimer-like dementia. In the primary results from ADAPT, naproxen and celecoxib did not prevent
In this ancillary ADAPT analysis, 2233 individuals were evaluated for change in risk of Alzheimer disease with self-reported, ongoing use of statins compared to non-lipid-lowering agent use. Over a follow-up period of 4 years, 24 participants converted to Alzheimer disease. In a model that adjusted for age, sex, education, and apolipoprotein E genotype, ongoing statin use was associated with a significant 67% reduction in the risk of Alzheimer disease (adjusted HR, 0.33; 95% CI, 0.11 to 0.98). Mean scores on the Mini-Mental State Examination at 1, 12, and 24 months were not different between statin users and nonusers.

Participants in the Religious Orders Study, a longitudinal clinical-pathologic study of Alzheimer disease, were 929 older Catholic clergy (mean age 75 years). All agreed to annual clinical evaluations and brain donation at time of death. During the follow-up period (up to 12 years), 191 persons developed Alzheimer disease. In a model that adjusted for age, sex, and education, statin use at baseline was not associated with incident Alzheimer disease as compared with nonuse (adjusted HR, 0.91; 95% CI, 0.54 to 1.52). Statins were not associated with change in global cognition or any of the cognitive domains. In a linear regression analysis, statins were not associated with the global Alzheimer disease pathology score. From logistic regression analysis, statin users were less likely to have amyloid plaques.

The Cardiovascular Health Cognition Study was an ancillary study of the Cardiovascular Health Study, a prospective population-based cohort study of risk factors for cardiovascular disease among community-dwelling adults ≥65 years of age. The main exposure was the use of statins as assessed by an annual medication inventory. Of the 2798 participants, 237 developed Alzheimer disease during the 6-year follow-up period. Compared with never use of lipid-lowering agents, ever use of statins was not associated with the risk of Alzheimer disease.
(adjusted HR, 1.21; 95% CI, 0.76 to 1.91). The model adjusted for demographic characteristics, cardiovascular and cerebrovascular disease status, and baseline cognition score.

The Cache County Study was an investigation of dementing illnesses and their genetic and environmental antecedents among the elderly population (≥65 years of age) of Cache County, Utah.27 The study began in 1995 with the enrollment of 5092 individuals. Approximately 3 years later, the investigators carried out a second wave of data collection, excluding participants who had earlier received diagnoses of dementia. For the exposed group, baseline statin use was confirmed by a visual inspection of bottles. Among the 3308 participants in the second wave cohort, 102 developed Alzheimer disease. In a model that adjusted for age, sex, education, diabetes, hypertension, and apolipoprotein E genotype, statin use at baseline did not predict incidence of Alzheimer disease (adjusted HR, 1.19; 95% CI, 0.35 to 2.96).

Results From Statistical Analysis

Figure 2 displays the forest plot of results from the individual studies and the meta-analysis. The estimate of the average effect of statin use on the risk of Alzheimer disease from the random-effects model was an HR of 0.76 (95% CI, 0.55 to 1.06). The chi-square test, where Q was > k–1 and p was < 0.10, suggested that statistical heterogeneity exists among the studies (Q = 9.806, df = 5, p = 0.081).32,33 The I² index of 49.011 indicated that almost half of the total variability among effect sizes was caused not by sampling error, but by true heterogeneity between studies. The heterogeneity in treatment effects across the included studies may be due to differences in the study populations (such as age of the participants), exposure (such as type or dose of statin), follow-up length, and other factors.

Subgroup analyses grouping studies by baseline versus ongoing assessment of exposure did not show a significant association between statin use and Alzheimer disease risk for the two
studies that assessed exposure at baseline only\textsuperscript{25,27} (HR, 0.96; 95% CI, 0.61 to 1.53) or the four studies with a more robust assessment of exposure\textsuperscript{22-24,26} (HR, 0.68; 95% CI, 0.43 to 1.07). The average effect size for the latter subgroup was numerically larger than that for the former subgroup. Subgroup analyses by length of follow-up did not show important differences in effect between the two studies with follow-up <5 years\textsuperscript{24,27} (HR, 0.66; 95% CI, 0.32 to 1.39) and the four studies with follow-up ≥5 years\textsuperscript{22,23,25,26} (HR, 0.78; 95% CI, 0.55 to 1.11).

Figure 3 is the funnel plot of the standard error by the log HR for the six included studies. Although interpretation is limited by the relatively small number of studies, the funnel plot did not suggest significant publication bias. The studies are distributed symmetrically about the combined average effect size. In the presence of bias, the bottom of the plot would show a higher concentration of studies on one side of the mean than on the other.

Data on change in cognitive function from baseline were only available from the ADAPT clinical trial cohort\textsuperscript{24} and the Religious Orders Study\textsuperscript{25} (results described earlier) and could not be combined due to differences in cognitive measures and time points.

**DISCUSSION**

This systematic review and meta-analysis synthesized the results from six prospective cohort studies that evaluated the risk of Alzheimer disease with statin use. The studies were of sufficiently similar designs that the results could be appropriately combined. To account for between-studies variability, a random-effects model was used to provide an estimate of the mean of a distribution of treatment effects across different study populations. The studies differed in terms of age of the participants, proportion of the population at increased risk for Alzheimer disease related to the apolipoprotein E genotype, and statin prescribing patterns over time and
across regions. The random-effects model predicted an average reduction in the risk of Alzheimer disease of 24% with statin use as compared with nonuse. The distribution of effect sizes ranged from a 45% risk reduction to a 6% risk increase. Although the 95% CI included the null value of 1.0, the non-significant result may be due to reduced statistical power. Two studies, in particular, had a low number of incident Alzheimer cases, especially in the exposed group. Of note, these studies had limited durations of follow-up, as short as 3 years.

The studies included in the meta-analysis selected samples using methods to minimize selection bias. Five of the six studies used pharmacy records or visual inspection of medication bottles to determine exposure status and reduce potential exposure misclassification. The exception was the ADAPT cohort, which used self-report of statin usage throughout the study to identify the exposed group and nonuse of any lipid-lowering medication at any time during the study for the comparison group. Alzheimer disease outcomes were assessed using structured criteria at regular intervals. All of the studies employed proportional hazards modeling to compute HRs, and the analyses controlled for confounding.

Early observational studies identified apparently protective effects of statins, with some estimates of relative risk reductions of more than two-thirds. In a cross-sectional analysis of data from three hospital pharmacy databases, the prevalence of diagnosed Alzheimer disease was 60% lower in patients taking statins than in the total patient population. In a nested case-control study using the United Kingdom-based General Practice Research Database, subjects who were prescribed statins had a 70% lower risk of dementia than those who were not on a lipid-lowering agent (odds ratio, 0.29; 95% CI, 0.13 to 0.63). A meta-analysis of seven retrospective observational studies suggested that statins lower the odds of developing cognitive impairment (pooled odds ratio, 0.43; 95% CI, 0.31 to 0.62).
Cross-sectional and case-control studies were excluded from this systematic review and meta-analysis as they are prone to more bias than prospective cohort studies. Different lengths of exposure periods for cases and controls in some studies could have resulted in biased estimates of the association between statin use and dementia or Alzheimer disease. If control subjects were observed longer than cases, then they had a higher probability of being prescribed statins. Indication bias, which exists when the indication for a drug being used or not used confounds the relationship between the drug and the disease, is another type of bias that could have resulted in a spurious protective effect. Physicians might less readily prescribe statins to individuals with early signs of cognitive impairment due to concerns with adherence or treatment complications. This can induce indication bias in which individuals with prevalent or early Alzheimer disease had less chance of receiving statins than the controls.

Any observational study, where the exposure is not randomly assigned, has the potential for confounding by indication and other sources of bias. Statin users are more likely to have multiple cardiovascular risk factors in addition to high serum cholesterol levels. Because these vascular risk factors are probably associated with greater risk of Alzheimer disease, the estimates of the association between statin exposure and risk of Alzheimer disease may have been biased toward the null. Several studies in this meta-analysis adjusted for baseline comorbid vascular disease but may not have achieved full control of confounding due to indication. Two studies relied on drug exposure obtained only at baseline,\textsuperscript{25,27} which may have resulted in some exposure misclassification with persons starting statin therapy during follow-up being classified as nonusers.

No randomized clinical trial has been conducted to evaluate the effect of statins in the prevention of Alzheimer disease. Two large cardiovascular trials, the Heart Protection Study and
the Prospective Study of Pravastatin in the Elderly (PROSPER), suggested that statins provided no benefit on cognition in individuals at risk for heart disease.\textsuperscript{35,36} However, neither study was designed to assess cognitive function. The Heart Protection Study evaluated simvastatin in the prevention of heart disease in 20,536 adults 40 to 80 years of age. Prevention of cognitive decline was a tertiary outcome measured by a telephone interview at final follow-up. No data on cognition at baseline were available. After 5 years of treatment, the rate of cognitive impairment or dementia did not differ between the simvastatin and placebo treatment groups. In PROSPER, pravastatin had no significant effect on cognitive function in 5804 older adults 70 to 82 years of age after 3 years of treatment.

This systematic review and meta-analysis provides direction for future research. Most of the included cohort studies started almost concurrently with the widespread use of statins and enrolled participants $\geq 65$ years of age. Therefore, the results do not reflect on any possible neuroprotective effect of statins occurring before age 65, or taken many years before persons would be likely to develop Alzheimer disease. Several years of statin use might be required for a reduction in risk of Alzheimer disease, or statin use might be effective only when treatment is taken for several years before the onset of symptoms. Statins may have a greater effect in persons with the apolipoprotein E4 genotype. Of the six included studies, the estimated relative risk reduction was largest in the ADAPT clinical trial cohort of at-risk individuals with at least one first-degree relative with Alzheimer disease. Also, the association between statin use and risk of Alzheimer disease might differ for lipophilic and hydrophilic statins. Statins are classified as either lipophilic (simvastatin, lovastatin, and cerivastatin) or hydrophilic (atorvastatin, pravastatin, and fluvastatin). Lipophilic statins pass the blood-brain barrier more efficiently than hydrophilic statins.\textsuperscript{37,38}
An effective preventive pharmacological treatment for Alzheimer disease would have important public health implications. Ideally, a randomized controlled trial would provide a more definitive evaluation of the effect of statins in protection against Alzheimer disease. Such a primary prevention trial might be prohibitively expensive without sufficient evidence of a protective association in specific populations. A large prospective cohort study with a prolonged follow-up period could address whether therapy started in middle life has an advantage over therapy started later in life. Other important questions to be evaluated include the characteristics of patients for whom therapy is beneficial and appropriate type, dose, and duration of statin treatment. Future studies should use annual measures of cognitive performance, such as the Modified Mini-Mental State Examination or the Alzheimer’s Disease Assessment Scale-cognitive subscale, over a long follow-up period to allow for accurate estimates of effects of statins on change in cognition.

New diagnostic criteria for Alzheimer disease were recently published, revising the NINCDS-ADRDA criteria that had been in place since 1984. Distinctive and reliable biomarkers of Alzheimer disease are now available through structural magnetic resonance imaging, molecular neuroimaging with positron emission tomography, and cerebrospinal fluid analyses. According to the new research criteria, the diagnosis of Alzheimer disease is made when there is both clinical evidence of the disease phenotype and structural/biological evidence of Alzheimer’s pathology (Appendix 2). The new criteria shift the focus in clinical research to detecting the disease as early as possible, optimally prior to the onset of dementia. These criteria should be applied in future studies to evaluate the effectiveness of statin treatment for delaying or preventing cognitive decline and Alzheimer disease.
REFERENCES


### APPENDIX 1: TABLES AND FIGURES

**Table 1. Prospective Studies on Statin Use and the Risk of Alzheimer Disease – Study Design and Results**

<table>
<thead>
<tr>
<th>Study (Year of Publication)</th>
<th>Design (Sample Size)</th>
<th>Exposure</th>
<th>Case Definition</th>
<th>Follow-up (No. of Events)</th>
<th>Variables Adjusted</th>
<th>Adjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li et al.(^{22}) (2010)</td>
<td>community cohort (United States) (3099)</td>
<td>ongoing statin use (≥3 filled prescriptions, pharmacy records)</td>
<td>NINCDS-ADRDA</td>
<td>mean 6 years (263 AD)</td>
<td>age, sex, race, education, baseline cognitive score, comorbid vascular diseases, BMI, smoking, and other LLA use</td>
<td>0.62 (0.40–0.97)</td>
</tr>
<tr>
<td>Haag et al.(^{23}) (2009)</td>
<td>community cohort (The Netherlands) (6992)</td>
<td>any statin during study (pharmacy records)</td>
<td>NINCDS-ADRDA</td>
<td>mean 9 years (466 AD)</td>
<td>age, sex, education, systolic blood pressure, cholesterol, diabetes, cardiovascular and cerebrovascular disease, BMI, smoking, and other LLA use</td>
<td>0.57 (0.37–0.90)</td>
</tr>
<tr>
<td>Sparks et al.(^{24}) (2008)</td>
<td>clinical trial cohort (United States) (2233)</td>
<td>ongoing statin use (self-reported use of statins at all visits)</td>
<td>NINCDS-ADRDA</td>
<td>4 years (24 AD)</td>
<td>age, sex, education, and APOE</td>
<td>0.33 (0.11–0.98)</td>
</tr>
<tr>
<td>Arvanitakis et al.(^{25}) (2008)</td>
<td>community cohort (United States) (929)</td>
<td>baseline statin use (visual inspection of bottles)</td>
<td>CERAD approach, NINCDS-ADRDA</td>
<td>up to 12 years (191 AD)</td>
<td>age, sex, and education</td>
<td>0.91 (0.54–1.52)</td>
</tr>
<tr>
<td>Rea et al.(^{26}) (2005)</td>
<td>community cohort (United States) (2798)</td>
<td>ever use of statins (annual visual inspection of bottles)</td>
<td>NINCDS-ADRDA</td>
<td>6 years (237 AD)</td>
<td>age, sex, education, alcohol use, coronary heart disease status, stroke status, and baseline MMSE score</td>
<td>1.21 (0.76–1.91)</td>
</tr>
<tr>
<td>Study (Year of Publication)</td>
<td>Design (Sample Size)</td>
<td>Exposure</td>
<td>Case Definition</td>
<td>Follow-up (No. of Events)</td>
<td>Variables Adjusted</td>
<td>Adjusted HR (95% CI)</td>
</tr>
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</tr>
<tr>
<td>Zandi et al.(^2^7) (2005) Cache County Study</td>
<td>community cohort (United States) (3308)</td>
<td>baseline statin use (visual inspection of bottles)</td>
<td>NINCDS-ADRDA</td>
<td>3 years (102 AD)</td>
<td>age, sex, education, hypertension, diabetes, and APOE</td>
<td>1.19 (0.35–2.96)</td>
</tr>
</tbody>
</table>

AD = Alzheimer disease; APOE = apolipoprotein E; BMI = body mass index; CERAD = Consortium to Establish a Registry for Alzheimer’s Disease; CI = confidence interval; HR = hazard ratio; MMSE = Mini-Mental State Examination; NINCDS-ADRDA = National Institute of Neurological and Communication Disorders and Stroke – Alzheimer Disease and Related Disorders Association.
Figure 1. Flow Diagram of Study Selection Process

272 publications from MEDLINE literature search

252 publications excluded after title/abstract screening:
- 18 Animal study
- 51 Mechanism of action study
- 7 Imaging or autopsy study
- 28 Review article
- 49 Comment/author reply
- 16 Ineligible study population
- 10 Ineligible study design
- 18 Ineligible outcome measure
- 55 Other/non-relevant article

20 potentially eligible studies/full-text publications screened

14 publications excluded after full-text screening:
- 11 No validated Alzheimer disease diagnosis
- 1 Study not prospectively designed
- 1 Study population not cognitively normal at baseline
- 1 Duplicate publication without additional data

6 studies included after title/abstract screening
Figure 2. Meta-Analysis of Six Prospective Cohort Studies on Statins and Risk of Developing Alzheimer Disease

<table>
<thead>
<tr>
<th>Study name</th>
<th>Statistics for each study</th>
<th>Hazard ratio and 95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard ratio</td>
<td>Lower limit</td>
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<tr>
<td>Li 2010</td>
<td>0.620</td>
<td>0.398</td>
</tr>
<tr>
<td>Haag 2009</td>
<td>0.570</td>
<td>0.365</td>
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<tr>
<td>Sparks 2008</td>
<td>0.330</td>
<td>0.111</td>
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<tr>
<td>Arvanitakis 2008</td>
<td>0.910</td>
<td>0.542</td>
</tr>
<tr>
<td>Rea 2005</td>
<td>1.210</td>
<td>0.763</td>
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<tr>
<td>Zandi 2005</td>
<td>1.190</td>
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<td></td>
<td>0.762</td>
<td>0.548</td>
</tr>
</tbody>
</table>

0.1 0.2 0.5 1 2 5 10

Favors Statin Use  Favors Nonuse
Figure 3. Funnel Plot of Standard Error by Log Hazard Ratio for Studies of Statins and Risk of Developing Alzheimer Disease
APPENDIX 2: REVISED DIAGNOSTIC CRITERIA FOR ALZHEIMER DISEASE

Probable AD: A plus one or more supportive features B, C, D, or E

Core diagnostic criteria

A. Presence of an early and significant episodic memory impairment that includes the following features:
   1. Gradual and progressive change in memory function reported by patients or informants over more than 6 months
   2. Objective evidence of significantly impaired episodic memory on testing
   3. The episodic memory impairment can be isolated or associated with other cognitive changes at the onset of AD or as AD advances

Supportive features

B. Presence of medial temporal lobe atrophy
   • Volume loss of hippocampi, entorhinal cortex, amygdala evidenced on MRI with qualitative ratings using visual scoring or quantitative volumetry of regions of interest

C. Abnormal cerebrospinal fluid biomarker
   • Low amyloid $\beta_{1-42}$ concentrations, increased total tau concentrations, or increased phospho-tau concentrations, or combinations of the three
   • Other well-validated markers to be discovered in the future

D. Specific pattern on functional neuroimaging with PET
   • Reduced glucose metabolism in bilateral temporal parietal regions
   • Other well-validated ligands

E. Proven AD autosomal dominant mutation within the immediate family
Definite AD: both criteria below

- Both clinical and histopathological (brain biopsy or autopsy) evidence of the disease
- Both clinical and genetic evidence of AD

AD = Alzheimer disease; MRI = magnetic resonance imaging; PET = positron emission tomography.

Source: Dubois et al. Lancet Neurol 2007;6:734-746 (Ref. 39)