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Statins and Brain Health: Alzheimer's and Cerebrovascular Disease Biomarkers in Older Adults

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Abstract

Background: Statins have been proposed to reduce the risk of Alzheimer's disease (AD).

Objective: Assess whether long-term statin use was associated with neuroimaging biomarkers of aging and dementia.

Methods: We analyzed neuroimaging biomarkers in 1160 individuals aged 65+ from the Mayo Clinic Study of Aging, a population-based prospective longitudinal study of cognitive aging.

Results: Statin-treated (5+ years of therapy) individuals had greater burden of mid- and late-life cardiovascular disease (p<0.001) than statin-untreated (≤3 months) individuals. Lower fractional anisotropy in the genu of the corpus callosum, an early marker of cerebrovascular disease, was associated with long-term statin exposure (p<0.035). No significant associations were identified between long-term statin exposure and cerebral amyloid or tau burden, AD pattern neurodegeneration, or white matter hyperintensity burden.

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Conflict of Interest Disclosures

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Conclusion: Long-term statin therapy was not associated with differences in AD biomarkers. Individuals with long-term statin exposure had worse white matter integrity in the genu of the corpus callosum, consistent with the coexistence of higher cerebrovascular risk factor burden in this group.

Keywords

Statins; Amyloid; Tau; Neurodegeneration; White matter; Alzheimer's disease; Cerebrovascular disease; Biomarkers; Magnetic resonance imaging (MRI); Positron emission tomography (PET)

Introduction

Statins, used by millions worldwide to lower cholesterol and prevent cardiac and cerebrovascular events, have been proposed as possible candidates for modifying the risk or progression of Alzheimer's disease (AD) and other causes of dementia. This hypothesis draws on the importance of cholesterol and other lipids in amyloid pathways [1], population genetics findings including the strong association of the apolipoprotein E (*APOE*) ε4 allele and other lipid-related genetic variants with AD [2–4], and animal and cellular experiments suggesting that statins may have roles in combating amyloid deposition, tau phosphorylation, and brain inflammation [5].

However, clinical studies of statins in aging and dementia have yielded only tenuous conclusions, with some observational data suggesting a protective association but other observational studies and randomized controlled trials not supporting this [6, 7]. In addition, existing studies using *in vivo* neuroimaging and postmortem neuropathology as outcomes have yielded conflicting results and have been limited by modest sample sizes and lack of generalizability [8–11]. The impact of statins on cognition with short- and long-term use is similarly controversial [12–16]. The inability to reconcile these contradictions in the literature underscores that the effects of statin use on brain health in the community setting are not well-understood.

Biomarkers provide robust *in vivo* measures of pathophysiologic processes central to aging and neurodegenerative disease [17]. Important neuroimaging biomarkers relevant for cognitive aging research in the general population are reflected in the Amyloid (A)/Tau (T)/Neurodegeneration (N) classification scheme [18, 19], and include measures of amyloid deposition via amyloid positron emission tomography (PET), tau pathology via tau PET, and neurodegeneration via FDG PET and structural magnetic resonance imaging (MRI). In addition, cerebrovascular disease is a well-established independent contributor to neurodegeneration and clinical decline in older adults [20–22], and MRI biomarkers with particular focus on white matter changes can be useful for assessing these changes [23–25]. Therapies to alter these biomarkers of brain health represent crucial potential avenues toward the ultimate goal of modifying the risk and progression of cognitive impairment in aging and dementia.

In this study, we analyzed multimodal neuroimaging data from a large, population-based sample of older adults to test the association of long-term statin use with biomarkers of aging and dementia.

Materials and Methods

Selection of Participants

The Mayo Clinic Study of Aging (MCSA) is a population-based prospective study among residents of Olmsted County, Minnesota. Complete details regarding the MCSA design are described elsewhere [26, 27]. In 2004, Olmsted County residents between the ages of 70 and 89 were identified for recruitment using the Rochester Epidemiology Project (REP) medical records linkage system [28, 29]. An age- and sex-stratified random sampling design was utilized to ensure that men and women were equally represented in each 10-year age stratum. The study was extended to include those aged 50 and older in 2012. Neuropsychological assessment, neuroimaging, and blood and cerebrospinal fluid biomarkers were assessed at selected visits. Clinical diagnoses incorporating available information were made by an expert consensus panel. All protocols were approved by the Mayo Clinic and Olmsted Medical Center Institutional Review Boards. Written informed consent was obtained from all participants or their surrogates. Our inclusion criteria included individuals over 65 years old with a completed amyloid PET scan and information on statin usage. Using these criteria, we identified 1160 elderly individuals for this study.

Classification of Statin Exposure

Current medications and the length of use were ascertained by trained study coordinators at each clinical visit. Individuals were classified as statin-untreated if their medication history at the time of clinical visit included no more than 3 months of statin therapy (n=604). Individuals on statin therapy for at least 5 years at the time of neuroimaging were defined as long-term statin-treated (n=556). Although excluded from the primary analyses, 174 individuals with intermediate duration of statin therapy (3 months-5 years) were investigated post-hoc for comparison (Supplementary Tables 1 and 2). For secondary analyses, the long-term statin-treated group was subdivided based on lipophilic (atorvastatin, fluvastatin, lovastatin, or simvastatin; n=497) or hydrophilic (pravastatin, rosuvastatin; n=58) characteristics of the medications [30], with one participant excluded from these analyses due to dual therapy with a lipophilic and hydrophilic statin.

Demographic and Clinical Data

Age, sex, and years of education for each participant were ascertained at clinical visit. *APOE* ε4 allele status (carrier vs. non-carrier) was determined through standard genotyping methods on blood samples [31]. Blood cholesterol and triglyceride levels were abstracted from REP data for selected participants from the clinical visit closest to the PET scan, with limits of no more than 2 years prior or 3 months after scan. Presence of midlife (40–64 years) vascular risk factors (diabetes, dyslipidemia, hypertension, and obesity) was assessed by trained nurses using the REP based on previously described criteria [32]. Smoking history (ever smoked) was determined by participant self-report. An index score of chronic, late-life cardiac, vascular, and metabolic conditions (hypertension, hyperlipidemia, cardiac arrhythmias, coronary artery disease, congestive heart failure, diabetes, and stroke) was calculated as a summation of the presence or absence of these conditions [20].

Neuroimaging Data

AD Imaging Biomarkers—The acquisition, processing, and summary measure details for AD biomarkers using PET and MRI scans acquired on the MCSA study participants are discussed elsewhere [33]. For amyloid PET, the global amyloid load was computed for each subject by calculating median uptake in the prefrontal, orbitofrontal, parietal, temporal, anterior cingulate, and posterior cingulate/precuneus regions of interest (ROIs) divided by the median uptake in the cerebellar crus gray matter ROI. For tau PET, a composite ROI was computed using median tau uptake in the entorhinal, amygdala, parahippocampal, fusiform, inferior and middle temporal ROIs divided by the cerebellar crus gray matter ROI. For FDG PET, a composite ROI uptake was computed from the median uptake in the angular gyrus, posterior cingulate, and inferior temporal cortical ROIs normalized by the median uptake in the pons. For each MRI, FreeSurfer (version 5.3) was used to estimate a composite measure of cortical thickness based on AD signature ROIs (entorhinal cortex and fusiform and inferior and middle temporal gyri).

Cerebrovascular Disease Imaging Biomarkers—We assessed white matter hyperintensities (WMHs) from FLAIR MRI and fractional anisotropy (FA) from diffusion tensor imaging (DTI) MRI. WMHs, representing a later consequence of the effects of cerebrovascular disease on white matter [24, 25], were segmented from FLAIR images as described previously [34, 35] and were normalized to yield a percentage of total intracranial white matter volume.

DTI sequences were processed as described previously [36] and were analyzed for measures of white matter microstructural degeneration as another indicator of cerebrovascular disease [37, 38]. We focused on FA of the corpus callosum, as we recently found that this measure was one of the most sensitive markers for ascertaining structural brain changes related to systemic vascular health [39]. Briefly, regional median FA and mean diffusivity (MD) were computed and registered using an in-house modified version of the JHU “Eve” white matter atlas. To address the potential for spurious effects from partial volume, voxels with MD > 2×10^{-3} or < 7×10^{-5} mm^2/s were excluded as mostly CSF or air, respectively, and regions with < 7 diffusion voxels in subject space were excluded as being too small to be reliably registered.

Of the 1160 individuals classified as statin-untreated or long-term statin-treated, all had amyloid PET data; 410 had tau PET data; 979 had FDG PET data; 1114 had MRI cortical thickness data; 485 had WMH data; and 945 had DTI data. For each biomarker, the continuous phenotypic measure was used for analysis to maximize statistical power for discovery.

Statistical Analyses

A combination of software packages was used for analyses, including SPSS Statistics version 22.0 (IBM Corp., Armonk, NY), RStudio: Integrated Development for R (RStudio, Inc., Boston, MA), and SAS version 9.4 (SAS Institute Inc., Cary, NC). Two-sided significance was set at α=0.05 (type I error rate). Standard summary measures were used to describe demographic and clinical characteristics for the sample, stratified by statin

exposure, with group comparisons obtained through *t* test for continuous variables and $\chi 2$ test for categorical variables. ANCOVA models adjusting for age and sex were used to test for associations between statin exposure and individual neuroimaging measures and to generate corresponding adjusted Cohen's *d* effect sizes. Prior to statistical analysis, the amyloid and tau PET and WMH phenotypes were transformed by natural log to ensure a normal distribution. To assess the robustness of associations of the statin exposure variable with neuroimaging measures, post-hoc sensitivity analyses were performed using a one-to-one age- (within 3 years) and sex-matched subset of 522 individuals and using conditional logistic regression to account for the matching.

Results

Of the 1160 elderly individuals included in this study, 558 (48%) were taking a statin at the time of their MCSA clinical visit. The most commonly prescribed statins were simvastatin (328/558 participants, 59%) and atorvastatin (136/558 participants, 24%). Eighty-six participants (7%) were on an alternative lipid-lowering agent, including 50 participants receiving concomitant statin and non-statin therapies. In the long-term statin-treated group, the median duration of statin therapy was 10 years and the maximum duration of therapy was 37 years.

Characteristics of the study sample are summarized in Table 1. Compared to the statin-untreated cohort, the long-term statin-treated cohort was older (79.1 years vs. 77.6 years, $p<0.001$) and included a higher proportion of males (58% vs. 50%, $p=0.007$). Mid- and late-life cardiovascular and metabolic conditions were significantly more common in statin-treated individuals ($p<0.001$), supportive of a higher chronic burden of vascular disease risk in this group (Table 1 and Supplementary Table 3). There was no significant difference between the groups for *APOE* ε4 allele status. In a subset of the sample with available laboratory data proximal to neuroimaging, long-term statin therapy was associated with lower LDL, consistent with the expected biochemical effects of therapy on lipid levels.

Long-term statin exposure was tested for association with neuroimaging biomarkers, adjusting for age and sex (Table 2). After adjustments there were no significant associations identified with global cortical amyloid PET burden, AD pattern tau PET burden, or AD pattern neurodegeneration assessed by hypometabolism on FDG PET and cortical thickness on MRI. Long-term statin exposure was also not associated with cerebrovascular disease assessed by WMHs.

Long-term statin therapy was associated with lower FA of the genu of the corpus callosum ($p=0.035$, Cohen's $d=0.14$), indicative of changes in white matter structural integrity related to cerebrovascular disease and consistent with the higher chronic burden of vascular disease risk identified in this group. This association was attenuated if the analyses were additionally adjusted for midlife hypertension and midlife diabetes ($p=0.09$, Cohen's $d=0.11$), suggesting that co-existing vascular risk factors may have partly explained the lower FA. In addition, presence of midlife dyslipidemia was more strongly associated with lower FA of the genu of the corpus callosum among statin-untreated individuals ($p=0.002$, Cohen's $d=0.27$) than in

the full sample, highlighting that cerebrovascular disease risk factors were likely driving the DTI changes.

The overall results were not different following stratification of the treatment group into lipophilic versus hydrophilic statin categories (Supplementary Table 4). No significant interaction of long-term statin therapy with *APOE* ε4 allele status was identified for any neuroimaging biomarker analyzed. There was a small negative correlation between the number of years of statin use (as a continuous variable) and WMH (r=0.17, p=0.01) but not with any other neuroimaging biomarker analyzed.

Sensitivity analyses using one-to-one age- and sex-matching (Supplementary Table 5) confirmed a direct effect of long-term statin exposure on lower FA in the genu of the corpus callosum (p=0.028), reinforcing that this association was not driven by age and sex differences. The sensitivity analyses identified no significant effects of the statin exposure variable on other neuroimaging biomarkers, further supporting the initial results.

Discussion

In this study from a community setting, older adults on long-term statin therapy exhibited no differences (adversely or protectively) in AD neuroimaging biomarkers compared to statin-untreated older adults. Long-term statin exposure was associated with worse white matter integrity in the genu of the corpus callosum, a finding that is consistent with the coexistence of higher cerebrovascular disease risk factor burden in this group. These results were not related to the relative lipophilicity (and presumed central nervous system penetration) of the prescribed medications. To our knowledge, this is the largest study to date of the effect of chronic statin therapy on neuroimaging measures of AD and cerebrovascular disease in older adults.

Statins have long been of interest in dementia broadly and in AD dementia in particular. Statins are highly effective on their intended target, lowering LDL cholesterol in treated individuals to levels far below those of untreated individuals (who by definition have normal cholesterol levels). Studies in animal and cellular model systems have suggested key roles for cholesterol and other lipids in generation of amyloid-β from its precursor, hyperphosphorylation of tau, and modulation of oxidative stress and inflammation [5, 40–43]. In addition, apolipoprotein E is the major cholesterol transporter in the brain [44], and the *APOE* ε4 allele is associated with dramatically increased risk of AD [45]. This data and more recently discovered susceptibility variants in other lipid-related genes, including *ABCA7* (ATP binding cassette, subfamily A, member 7), *CLU* (clusterin), and *SORL1* (sortilin-related receptor 1), have intensified the focus on the lipid-AD relationship [4]. However, most cholesterol in the brain is synthesized *de novo*, and the exact relationship between circulating lipid levels and brain lipid metabolism is unclear [46]. In addition, most of the molecular data on statins is based on high dose exposure in an experimental setting, conditions which may not allow translation to the clinical setting with typical dosing and intra-class variation in drug permeability and bioavailability in the central nervous system.

Previous clinical studies of lipids and statins in aging and dementia have historically been difficult to reconcile [6–11, 30, 47–54]. Proposed explanations for the heterogeneity of any medication effects have included variation in the type of statin [52, 53, 55], genetic background [52], age of intervention [51], degree of cognitive impairment [10], and race/ethnicity and gender [53]. Our findings from a large, population-based sample support a unifying hypothesis – namely, that chronic statin use in mid- to late-life does not appear to impact neuroimaging biomarkers of typical AD but may have the capacity to influence brain structure and function and the resultant risk of dementia through modifying cerebrovascular health. This model accounts for the conflicting findings from observational studies and the lack of evidence for a protective effect of statins in randomized controlled trials [6, 7] by recognizing that dementia as an endpoint is heterogeneous as to underlying etiology. As a result, putative effects previously described for dementia as an umbrella diagnosis or for assorted subsets of the aging population may have reflected underlying heterogeneity in vascular disease burden rather than a mechanistic connection to AD pathophysiology.

Our study was not a prospective randomized controlled trial, and thus was not a formal test for causation. Similarly, our study design was not equipped to directly assess whether individuals treated with statins would have displayed different biomarker profiles had treatment not been initiated. Our analyses focused on cross-sectional clinical and neuroimaging data, but future efforts using a longitudinal framework and tracking blood lipid levels, neuroimaging biomarkers, and cognitive function over time would help to further characterize the relationship among statins, circulating lipid levels, neuroimaging biomarkers, and cognition. Another limitation of this work is that we were not able to systematically consider variations in statin dose (including categories of therapy intensity) or indications for therapy (including primary vs. secondary prevention). In addition, we did not include younger individuals in the sample, and as a result cannot rule out the possibility for statin therapy in earlier life stages to be associated with changes in AD neuroimaging biomarkers. Finally, based on power calculations, this study was capable of detecting Cohen's *d* effect sizes between 0.08–0.14 for the main analyses, but we cannot exclude the possibility for smaller effect sizes implicating statins as a risk or protective factor on neuroimaging biomarkers.

Given that comorbid neuropathological features are the rule rather than the exception in aging and neurodegenerative disease [56], strategies to prevent and treat dementia may ultimately require a systematically determined combination of interventions to address individualized susceptibility and protective factors related to genetics, cognitive reserve, and concomitant medical conditions and drug exposures [57]. AD serves as a particularly germane example in that key biomarker abnormalities can be initiated independently early in the disease but in later stages can display interactions which accelerate progression [17, 58, 59]. As such, the insights from this study may be crucial in facilitating targeting of a commonly used medication class toward modulating brain biomarkers of cerebrovascular health and away from the expectation of changes in biomarkers of typical AD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Summary characteristics of the sample by statin exposure classification

	Statin-Untreated[a] (0–3 months) N=604	Statin-Treated[a] (≥5 years) N=556	*p*-value[b]
Demographics[c]			
Age (years)	77.6 (7.8)	79.1 (7.3)	<0.001
Males	305 (50%)	325 (58%)	0.007
Education (years)	14.7 (2.8)	14.4 (2.9)	0.088
Vascular risk factors			
Mid-life diabetes [68,32]	15 (3%)	57 (11%)	<0.001
Mid-life dyslipidemia [68,32]	237 (44%)	391 (75%)	<0.001
Mid-life hypertension [68,32]	179 (33%)	242 (46%)	<0.001
Mid-life obesity [98,64]	147 (29%)	195 (40%)	<0.001
Prior smoking	258 (43%)	276 (50%)	0.018
Late-life cardiovascular and metabolic disease index	1.63 (1.36)	3.13 (1.39)	<0.001
Clinical data			
***APOE* ε4 positive [5,6]**	160 (27%)	167 (30%)	0.17
Cognitively unimpaired [4,4]	502 (84%)	440 (80%)	0.072
Mild cognitive impairment [4,4]	86 (14%)	93 (17%)	
Dementia [4,4]	12 (2%)	19 (3%)	
LDL (mg/dL) [236,53]	111.3 (32.3)	82.4 (23.2)	<0.001
Triglycerides (mg/dL) [236,53]	125.1 (55.2)	132.0 (61.8)	0.093

[a] Values are displayed as mean (standard deviation) for continuous variables and number (percentage) for categorical variables

[b] Via *t* test for continuous variables and $\chi 2$ test for categorical variables

[c] Brackets indicate the number of subjects with missing data, ordered as [statin-untreated, statin-treated]. When no brackets are listed, this indicates that complete data was obtained for that variable.

Table 2.

Associations of long-term statin treatment with neuroimaging biomarkers of aging and dementia

	Statin-Untreated[a] (0–3 months) N=604	Statin-Treated[a] (≥5 years) N=556	*p*-value	Cohen's *d*[d]
PiB PET SUVR[b,c]	1.62 (0.46)	1.65 (0.45)	0.95	0
Tau PET SUVR[b] **[395,355]**	1.22 (0.13)	1.24 (0.15)	0.54	0.06
FDG PET SUVR [89,92]	1.52 (0.16)	1.49 (0.16)	0.33	0.06
MRI Cortical Thickness [17,29]	2.64 (0.16)	2.61 (0.16)	0.21	0.08
WMH Percentage[b] **[344,331]**	4.02 (3.69)	4.50 (3.98)	0.83	0.02
FA Corpus Callosum Body [106,109]	0.579 (0.049)	0.571 (0.049)	0.30	0.07
FA Corpus Callosum Genu [106,109]	0.581 (0.051)	0.569 (0.054)	0.035	0.14

[a] Values are displayed as unadjusted mean (standard deviation)

[b] Phenotypes were log-transformed for association testing

[c] Brackets indicate the number of subjects with missing data, ordered as [statin-untreated, statin-treated]. When no brackets are listed, this indicates that complete data was obtained for that variable.

[d] Effect sizes are adjusted for age and sex