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Effects of Statins on Memory, Cognition, and Brain Volume in the Elderly

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ABSTRACT

BACKGROUND There is widespread consumer concern that statin use may be associated with impaired memory and cognitive decline.

OBJECTIVES This study sought to examine the association between statin use and changes in memory and global cognition in the elderly population over 6 years and brain volumes over 2 years. Interactions between statin use and known dementia risk factors were examined.

METHODS Prospective observational study of community-dwelling elderly Australians age 70 to 90 years (the MAS [Sydney Memory and Ageing Study], n = 1,037). Outcome measures were memory and global cognition (by neuropsychological testing every 2 years) and total brain, hippocampal and parahippocampal volumes (by magnetic resonance) in a subgroup (n = 526). Analyses applied linear mixed modeling, including the covariates of age, sex, education, body mass index, heart disease, diabetes, hypertension, stroke, smoking, and apolipoprotein Eε4 carriage. Interactions were sought between statin use and dementia risk factors.

RESULTS Over 6 years there was no difference in the rate of decline in memory or global cognition between statin users and never users. Statin initiation during the observation period was associated with blunting the rate of memory decline. Exploratory analyses found statin use was associated with attenuated decline in specific memory test performance in participants with heart disease and apolipoprotein Eε4 carriage. There was no difference in brain volume changes between statin users and never users.

CONCLUSIONS In community-dwelling elderly Australians, statin therapy was not associated with any greater decline in memory or cognition over 6 years. These data are reassuring for consumers concerned about statin use and risk of memory decline. (J Am Coll Cardiol 2019;74:2554–68) Crown Copyright © 2019 Published by Elsevier on behalf of the American College of Cardiology Foundation. All rights reserved.

Hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) are among the most widely prescribed medication classes (1). Recent recommendations have reduced lipid thresholds for statin prescription (2), with strong evidence for benefit and mortality reduction in cardiovascular disease, stroke, diabetes, renal disease, and genetic lipid disorders (3–5). Importantly, statin use is not associated with risk of major adverse health events (5).

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The majority of trials demonstrating benefit were conducted in mid-life, with the exception of 1 trial that showed a 15% reduction in major cardiovascular events and coronary heart disease death with pravastatin (6). Furthermore, few trials reported memory or cognition as a main outcome (6–8) as reviewed elsewhere (9).

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Consumer concerns regarding potential effects on cognition exist, compromising acceptance or adherence to statin medications. Statin-related memory and/or cognitive changes are the second most frequently reported statin adverse effect (10). The U.S. Food and Drug Administration requires a label warning of cognitive adverse effects based on cases reported (11). Anecdotal cases reported variable onset and rechallenge effects (12–14). In contrast, longitudinal studies show no adverse association between statins and cognition, in the cognitively intact (15–18), in impaired cognition (19–23), or for memory change (15,24). These studies have limitations including simple measurements (16,17,19–21), control subjects commencing statins during observation (15,16,18–20,22), and short observation (17–20,23). Our recent attempt at meta-analysis in elderly cohorts was challenged by divergent neuropsychological testing methods precluding pooled analyses (9); the summative review found no beneficial or detrimental associations between statins and cognition in the elderly cohort with normal baseline cognition, impaired cognition, or with incident dementia (9).

A number of randomized statin trials reported memory (7,25–27) or global cognition (6,7,28) in participants that were cognitively intact or had baseline cognitive impairment or dementia (17,29–31). Most found no association between statins and change in test measures over 1 to 12 months. However, 2 6-month trials found minor decrements in memory and global cognition in younger participants with simvastatin (26) and lovastatin (28). Limitations include short duration (17,25–27,31), few elderly participants (25–27,31), small numbers (17,25–27,31), limited cognitive measures (17,29–31), exclusion of participants with dementia risk factors (17,25,26,29,30), lack of reporting of dementia risk factors (27,31), or lack of adjustment for these risk factors (17,25,27,28,31).

The only long-term randomized trial of substantial duration in the elderly population is the PROSPER (Prospective Study of Pravastatin in Elderly at Risk), which found no difference in the change in Mini Mental State Examination (6) or working or declarative memory test scores (7). Important considerations limit this study's extrapolation to the general elderly population including lack of inclusion of dementia risk factors as covariates and selection bias. For example, there is evidence that trials in elderly participants are nonrepresentative (32). Furthermore, the hydrophilic pravastatin does not cross the blood-brain barrier, unlike other statins. The simvastatin Heart Protection Study found no impact on incident minor cognitive impairment or dementia after 5.2 years follow-up in participants age 40 to 80 years, but the study did not control for dementia risk factors and dementia ascertainment did not follow the rigorous standards of cognitive assessment required currently (33). These considerations temper whether findings can be extrapolated to lipophilic statins or to the general elderly population.

Therefore, the relationship between statin use and changes in memory or cognition in the elderly population remains uncertain and worthy of examination. Because further long-term randomized controlled trials of statins examining this issue are unlikely due to their high cost, rigorous longitudinal studies examining statin use and cognition in the elderly population, of reasonable duration and controlling for dementia risk factors, are an appropriate recourse. We report the changes in memory and global cognition with regard to statin use over 6 years of observation and brain volumes over 2 years in the MAS (Sydney Memory and Ageing Study), a longitudinal observational study of cognition in community-dwelling, nondemented elderly Australians (34–36).

ABBREVIATIONS AND ACRONYMS

APOE = apolipoprotein E
BMI = body mass index
GM = gray matter
OR = odds ratio
RAVLT = Rey Auditory Verbal Learning Test
WM = white matter

METHODS

PARTICIPANTS. The MAS is a longitudinal population-derived cohort age 70 to 90 years at baseline recruited through the compulsory electoral roll (n = 1,037) (34–36). Exclusion criteria were insufficient English for assessments, a dementia diagnosis, major neurological or psychiatric disease, and progressive malignancy. The Mini Mental State Examination was used to screen participants, and those with a score <24 were excluded. The study was approved by the institutional Human Research and Ethics Committee. Participants gave written informed consent.

Data were collected every 2 years on 4 occasions over a 6-year period by psychologists and nurses. Participants completed standardized questionnaires recording all medical conditions and sociodemographics. Non-English-speaking background was determined by English literacy acquired after 9 years of age (34,37).

The presence of cardiac and cerebrovascular disease and hypertension were ascertained by medical practitioner diagnosis; type 2 diabetes mellitus (diabetes) by medical practitioner diagnosis, report of glucose-lowering medications, or a fasting glucose level >7.0 mmol/l. Weight and height were measured and body mass index (BMI) was calculated (kg/m^2). Blood pressure was measured twice in the recumbent position after at least 5 min of rest.

STATIN EXPOSURE ASCERTAINMENT. All medications and duration of use, particularly statins, were ascertained during each assessment. Participants were categorized as follows: 1) statin ever use versus never use; 2) continuous statin use during observation versus never use; 3) specific statins (simvastatin, pravastatin, and atorvastatin) versus never use; and 4) statin initiation during observation period.

NEUROPSYCHOLOGICAL MEASURES. A priori, 2 endpoints—memory and global cognition—were selected as the primary outcome measures. A comprehensive assessment of global cognition and memory was developed to overcome limitations of previous work employing only basic screening measures lacking in sensitivity to detect subtle cognitive impairment and decline. Global cognition was represented by 12 cognitive tests for 5 cognitive domains, as follows and was described elsewhere (34,36,38,39).

Memory domain was represented by verbal and visual memory tasks incorporating multiple measures of new learning, short- and long-term recall, in line with recent work suggesting this comprehensive approach enhances detection of mild cognitive impairment (40). Five memory tests were employed: total learning (Rey Auditory Verbal Learning Test-total [RAVLT-total]); short-delayed recall (RAVLT-6 item); long-delayed recall (RAVLT-7 item) (41); Benton Visual Retention Test recognition (42); Logical Memory story A (delayed recall) (43). Raw scores were converted to *z*-scores, based on the mean ± SD of a normal cognition reference sample. Memory domain score was calculated by averaging the component test *z*-scores.

Global cognition evaluated memory plus processing speed (Wechsler Adult Intelligence Scale-III Digit Symbol-Coding [42] and Trail Making Test part A [44]), language (Category Fluency Test [Animals] [45] and Boston Naming Test [30-item version] [46]), visuospatial ability (Block Design from the Wechsler Adult Intelligence Scale-Revised [47]), and executive function (Letter Fluency Test [48] and Trail Making Test part B [44]). The global cognition domain score was calculated by obtaining *z*-scores for each of the component tests (including memory), then averaging and transforming the *z*-scores using the cognitively normal baseline sample.

LABORATORY MEASURES. Blood was collected after a 10-h overnight fast. Assay measurements were plasma glucose (glucose oxidase method; Beckman Coulter, Fullerton, California); total cholesterol, high-density lipoprotein cholesterol, triglycerides, and urate levels (timed-endpoint method; Beckman Coulter); low-density lipoprotein cholesterol (Friedewald equation); homocysteine levels (reverse-phase high-performance liquid chromatography; BioRad, Munich, Germany); highly sensitive C-reactive protein levels (near-infrared particle immunoassay rate; Beckman Coulter Synchron LXi, Beckman Coulter), as described (35,49). Non-normally distributed variables were transformed logarithmically (high-density lipoprotein-cholesterol, triglycerides, C-reactive protein, vitamin B_{12}, insulin) or normalized by rank-order scores (glucose). Apolipoprotein E (APOE) genotype was determined by deoxyribonucleic acid analysis of peripheral blood or saliva (Taqman, Applied Biosystems Inc., Foster City, California), as described elsewhere (39).

STRUCTURAL BRAIN MAGNETIC RESONANCE IMAGING AND VOLUMETRY. Brain magnetic resonance imaging was offered to all participants at baseline: 529 accepted and 408 had repeat magnetic resonance at 2 years, using the 3-T Intera Quasar or 3-T Achieva Quasar Dual scanner (Philips Medical Systems, Amsterdam, the Netherlands) as described elsewhere (36,39). Acquisition parameters (T_1-weighted structural scans) were repetition time = 6.39 ms, echo time = 2.9 ms, flip angle = 8°, matrix size = 256 × 256, field of view = 256 × 256 × 190, and slice thickness = 1 mm with no gap. Gray matter (GM), white matter (WM), cerebrospinal fluid, and intracranial volume were measured. Total brain volume was defined as the sum of GM and WM. To ensure that no error was introduced by scanner change, 5 participants were imaged on both scanners within 2 months; GM, WM, cerebrospinal fluid, and intracranial volume were similar between the 2 instruments (50).

Regional GM volumes were calculated using 90 parcellations, delineated by the Automated Anatomical Labelling atlas (51) using voxel-based morphometry approach (52) (Statistical Parametric Mapping software; Wellcome Department of Imaging Neuroscience, London, United Kingdom). Using Markov random field option, T_1-weighted images were delineated by region, using the McConnell Brain Imaging

TABLE 1 Baseline Demographics of the MAS Participants: Statin Ever Users Versus Never Users

	Statin Never Users (n = 395)		Statin Ever Users (n = 642)		p Value
Descriptives					
Age, yrs	79.3 ± 4.8	395	78.6 ± 4.8	642	0.016
Male	227 (57.5)	395	345 (71.9)	642	0.24
Duration of statin use, yrs	–	–	9.1 ± 6.9	472	0.26
Years of education	11.7 ± 3.5	395	11.5 ± 3.5	642	0.40
Physical measures					
Weight, kg	74.3 ± 15.8	382	77.4 ± 15.8	636	0.002
BMI, kg/m^2	26.0 ± 4.5	382	27.9 ± 4.9	630	<0.0001
Systolic BP, mm Hg	146 ± 22	383	144 ± 20	632	0.30
Diastolic BP, mm Hg	83 ± 11	383	81 ± 11	632	0.002
Prevalence of vascular diseases and dementia risk factors					
Heart disease	84 (8.1)	394	268 (42.1)	637	<0.0001
Diabetes	27 (6.9)	394	96 (15.0)	638	<0.0001
Stroke	6 (1.5)	393	35 (5.5)	634	0.002
TIA	27 (6.9)	366	42 (6.7)	623	0.84
Hypertension	196 (49.7)	394	433 (67.8)	629	<0.001
Antihypertensives, yrs	10.7 ± 10.8	193	12.6 ± 10.7	423	0.043
Ever smoked	200 (50.6)	395	359 (56.1)	640	0.09
APOEε4 gene carrier	72 (19.7)	366	149 (24.2)	614	0.11
Laboratory measures					
Glucose, mmol/l	5.7 ± 0.9	345	6.0 ± 1.3	585	<0.001
Total cholesterol, mmol/l	5.2 ± 0.9	346	4.5 ± 1.0	587	<0.001
HDL cholesterol, mmol/l	1.5 ± 0.5	346	1.4 ± 0.4	585	<0.001
LDL cholesterol, mmol/l	3.2 ± 0.8	346	2.6 ± 0.9	582	<0.001
Triglycerides, mmol/l	1.0 ± 1.0	346	1.2 ± 0.6	587	<0.001
C-reactive protein, mg/l	3.2 ± 5.9	347	3.0 ± 5.2	586	0.38
Insulin, μU/ml	13.8 ± 5.7	286	16.5 ± 8.4	511	<0.001
Vitamin B_{12}, pmol/l	233 ± 443	338	200 ± 318	560	0.23
Uric acid, mmol/l	0.30 ± 0.10	273	0.31 ± 1.0	449	0.10
Cognitive domain measures, *z*-scores					
Memory	−0.56 ± 1.24	390	−0.50 ± 1.18	636	0.42
Global cognition	−0.78 ± 1.43	393	−0.69 ± 1.34	639	0.28
Specific memory test scores					
Logical memory	−0.49 ± 1.18	393	−0.41 ± 1.16	641	0.27
RAVLT—total	−0.41 ± 1.16	391	−0.35 ± 1.15	637	0.51
RAVLT—6 item	−0.43 ± 1.18	391	−0.35 ± 1.15	637	0.28
RAVLT—7 item	−0.37 ± 1.18	391	−0.34 ± 1.12	637	0.69
BVRT	−0.35 ± 1.27	392	−0.36 ± 1.16	635	0.99
Other cognitive domains					
Attention and/or processing speed	−0.45 ± 1.29	389	−0.39 ± 1.17	632	0.43
Language	−0.79 ± 1.50	392	−0.72 ± 1.55	638	0.47
Executive function	−0.54 ± 1.37	366	−0.41 ± 1.20	584	0.12
Visuospatial function	−0.36 ± 1.08	394	−0.32 ± 1.10	640	0.61

Values are mean ± SD, n, or n (%). Continuous variables were compared by analysis of variance and categorical variables by chi-square tests. Non-normally data were transformed for comparisons (logarithmic transformation: triglycerides, insulin, C-reactive protein, and uric acid; rank order transformation: glucose).

APOEε4 = apolipoprotein Eε4; BMI = body mass index; BP = blood pressure; BRVT = Benton Visual Retention Test (recognition); HDL = high-density lipoprotein; LDL = low-density lipoprotein; RAVLT = Rey Auditory Verbal Learning Test; RAVLT-total = total learning; RAVLT-6 item = short delayed recall; RAVLT-7 item = long delayed memory; TIA = transient ischemic attack.

Center's ICBM152 atlas. A series of customized templates were generated by iterative registration (53) with images registered to group templates to create the modulated warped tissue class images. Spatial normalization of GM to the Montreal Neurological Institute space was achieved using an affine transformation to the ICBM152 template. The 12-mm full width at half maximum Gaussian kernel smoothing was performed to generate the voxel-based GM volumes.

TABLE 2 Statin Use and Global Cognition, Memory Domain, and Specific Memory Test Scores: Associations at Baseline and With Changes Over 6 Years of Observation

	Model 1*						Model 2†					
	Baseline			Cognitive Decline Over 6 yrs			Baseline			Cognitive Decline Over 6 yrs		
Group Comparison‡	B§‖	SE	p Value	B¶#	SE	p Value	B§‖	SE	p Value	B¶#	SE	p Value
Statin ever users vs. never users												
Memory domain	0.040	0.069	0.56	−0.022	0.025	0.39	0.117	0.083	0.16	−0.012	0.027	0.65
Global cognition	0.083	0.078	0.28	0.010	0.030	0.73	0.133	0.089	0.14	0.022	0.032	0.49
Specific test score												
Logical memory	0.059	0.068	0.39	−0.035	0.027	0.19	0.085	0.083	0.31	−0.018	0.029	0.54
RAVLT—total	0.012	0.062	0.85	−0.017	0.026	0.51	0.074	0.076	0.33	−0.013	0.028	0.64
RAVLT—6 item	0.049	0.068	0.47	−0.032	0.026	0.22	0.111	0.082	0.17	−0.028	0.029	0.33
RAVLT—7 item	0.021	0.066	0.75	−0.008	0.025	0.74	0.040	0.079	0.61	0.010	0.027	0.70
BVRT	−0.017	0.068	0.81	0.015	0.034	0.67	0.099	0.080	0.22	0.012	0.037	0.75
Continuous statin users vs. never users												
Memory domain	0.055	0.075	0.46	−0.028	0.027	0.30	0.219	0.093	0.019	−0.023	0.029	0.43
Global cognition	0.097	0.085	0.25	0.025	0.031	0.43	0.239	0.098	0.015	0.026	0.034	0.44
Specific test score												
Logical memory	0.069	0.074	0.35	−0.032	0.029	0.27	0.156	0.093	0.09	−0.010	0.032	0.76
RAVLT—total	0.027	0.068	0.69	−0.031	0.028	0.28	0.156	0.085	0.07	−0.034	0.030	0.25
RAVLT—6 item	0.058	0.074	0.44	−0.038	0.028	0.17	0.183	0.092	0.047	−0.038	0.030	0.21
RAVLT—7 item	0.055	0.072	0.45	−0.024	0.027	0.37	0.159	0.089	0.07	−0.015	0.029	0.60
BVRT	−0.016	0.073	0.83	0.020	0.038	0.61	0.147	0.088	0.10	0.006	0.041	0.89
Simvastatin users vs. never users												
Memory domain	0.030	0.069	0.664	−0.044	0.035	0.21	0.103	0.079	0.19	−0.046	0.039	0.24
Global cognition	0.008	0.071	0.910	−0.025	0.039	0.51	0.102	0.077	0.18	−0.026	0.041	0.52
Specific test score												
Logical memory	0.024	0.077	0.759	−0.003	0.038	0.94	0.098	0.089	0.27	0.02	0.041	0.64
RAVLT—total	0.024	0.068	0.728	−0.036	0.036	0.33	0.044	0.078	0.57	−0.035	0.039	0.38
RAVLT—6 item	0.097	0.074	0.189	−0.063	0.037	0.09	0.121	0.085	0.15	−0.060	0.040	0.14
RAVLT—7 item	0.016	0.071	0.826	−0.036	0.035	0.31	0.024	0.081	0.77	−0.025	0.039	0.52
BVRT	−0.024	0.085	0.780	−0.015	0.050	0.76	0.174	0.097	0.07	−0.073	0.053	0.17
Pravastatin users vs. never users												
Memory domain	0.006	0.112	0.96	−0.055	0.059	0.35	0.198	0.129	0.13	−0.071	0.064	0.27
Global cognition	−0.152	0.114	0.18	0.077	0.065	0.24	−0.126	0.126	0.32	0.081	0.068	0.23
Specific test score												
Logical memory	−0.030	0.124	0.81	−0.045	0.063	0.48	0.100	0.146	0.50	−0.040	0.069	0.56
RAVLT—total	−0.018	0.109	0.87	−0.03	0.06	0.62	0.157	0.128	0.22	−0.041	0.066	0.54
RAVLT—6 item	0.053	0.118	0.66	0.001	0.061	0.98	0.300	0.138	0.03	−0.043	0.067	0.52
RAVLT—7 item	0.017	0.114	0.88	−0.052	0.059	0.37	0.200	0.133	0.13	−0.073	0.065	0.26
BVRT	−0.023	0.138	0.87	−0.067	0.085	0.43	−0.007	0.157	0.96	−0.024	0.089	0.79

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Three brain regions of interest were selected a priori: total brain volume and hippocampal and parahippocampal volumes.

STATISTICAL ANALYSES. Statin-use categories were compared using analysis of variance for continuous variables, and chi-square tests were used for categorical variables.

In the first set of analyses, linear mixed modeling examined the relationships between statin ever use and never use and baseline performance in memory and global cognition. Study wave (baseline: wave 1; 2 years: wave 2; 4 years: wave 3; 6 years: wave 4) was treated as a continuous variable representing time. Random effects for the intercept and wave were included. Statin ever use and wave were entered as fixed effects. The coefficient for the fixed effect of statin use was interpreted as the difference between statin ever users and never users at baseline: positive values indicated statin users had higher test scores than did never users. The coefficient for ever use × time interaction was interpreted as the average difference between ever users and never users in the rate of memory change per 2 years. A positive coefficient indicated statin ever users had slower cognitive decline per wave than did nonusers. Analyses were repeated comparing statin never users and

TABLE 2 Continued

	Model 1*						Model 2†					
	Baseline			Cognitive Decline Over 6 yrs			Baseline			Cognitive Decline Over 6 yrs		
Group Comparison‡	B§‖	SE	p Value	B¶#	SE	p Value	B§‖	SE	p Value	B¶#	SE	p Value
Atorvastatin users vs. never users												
Memory domain	−0.017	0.062	0.78	−0.006	0.03	0.84	0.007	0.069	0.92	−0.010	0.033	0.77
Global cognition	0.000	0.062	1.00	−0.012	0.033	0.71	0.008	0.067	0.90	−0.029	0.034	0.40
Specific test score												
Logical memory	0.003	0.07	0.96	−0.012	0.033	0.72	0.037	0.080	0.65	−0.002	0.036	0.96
RAVLT—total	−0.071	0.062	0.25	−0.019	0.031	0.55	−0.023	0.069	0.75	−0.033	0.034	0.33
RAVLT—6 item	−0.027	0.067	0.69	0.008	0.032	0.80	−0.000	0.075	0.99	0.007	0.035	0.85
RAVLT—7 item	−0.015	0.064	0.81	−0.015	0.031	0.62	−0.001	0.072	0.99	−0.012	0.033	0.71
BVRT	0.106	0.079	0.18	0.038	0.043	0.37	0.131	0.089	0.14	0.038	0.046	0.40
Statin initiation users vs. never users												
Memory domain	−0.016	0.067	0.81	0.031	0.027	0.25	−0.054	0.073	0.46	0.060	0.029	0.038
Global cognition	0.019	0.072	0.79	0.006	0.028	0.83	−0.018	0.076	0.81	0.030	0.030	0.31
Specific test score												
Logical memory	−0.023	0.079	0.77	0.024	0.032	0.46	−0.004	0.086	0.96	0.024	0.034	0.49
RAVLT—total	−0.102	0.070	0.15	0.039	0.029	0.17	−0.139	0.076	0.07	0.056	0.030	0.07
RAVLT—6 item	0.010	0.074	0.89	0.003	0.030	0.91	−0.072	0.080	0.36	0.036	0.032	0.26
RAVLT—7 item	−0.048	0.070	0.49	0.052	0.028	0.06	−0.089	0.075	0.24	0.092	0.030	0.002
BVRT	0.093	0.101	0.36	−0.017	0.042	0.68	0.068	0.106	0.52	0.004	0.044	0.92

B is the regression coefficient. SE is the standard error of B. The p value is the level of statistical significance for the rejection of the null hypothesis B = 0. *Model 1's covariates included age, sex, and education. †Model 2's covariates included age, sex, education, non-English-speaking background, body mass index, ever smoker, heart disease, diabetes, stroke, hypertension, systolic blood pressure, and apolipoprotein Eε4 genotype carriage. ‡Sample sizes for the groups in each comparison are as follows. Model 1: statin ever users n = 642, never users n = 395; continuous statin users n = 444, never users n = 385; specific statins: simvastatin n = 162; pravastatin n = 44, atorvastatin n = 232; statin initiation n = 117, never users n = 394. Model 2: statin ever users n = 489, never users n = 273; continuous statin users n = 325, never users = 268; specific statins users: simvastatin n = 138; pravastatin n = 37, atorvastatin n = 204; statin initiation n = 99, never users n = 331. §Regression coefficient reflects the mean difference in cognitive test performance at baseline between the groups, adjusting for model covariates. Differences are in standardized units of the cognitive test. Specifically, the coefficient is the mean baseline cognitive test performance of the first group (e.g., statin users) minus the mean baseline cognitive test performance for never users, where positive values indicate the first group had better average baseline performance than never users ‖For statin initiation results, the regression coefficient reflects the average shift in baseline cognitive test performance for participants that initiated statins, relative to the baseline performance of never users, adjusting for model covariates. Positive values indicate that participants initiating statins had better cognitive test performance on average than did never users, at the wave at which statin use was initiated ¶Regression coefficient reflects the difference between groups in their average change in cognitive test performance per year, in standardized units, adjusting for model covariates. Specifically, it is the annual rate of change in cognitive test performance for the first group (e.g., statin users) minus the annual rate of change in cognitive test performance for never users. Positive values indicate that the first group, when compared with never users, had a slower rate of decline in cognitive test performance, per year (in standardized units) #For statin initiation, the regression coefficient represents the difference in the annual rate of change in cognitive test performance for participants initiating statins compared with statin never users, after statins were initiated (adjusting for model covariates). Specifically, it is the average annual rate of change in cognitive test performance for participants that initiated statins minus the average annual rate of change in cognitive test performance in statin never users. Positive values indicate that after participants initiated statins, their rate of cognitive decline per year was on average, slower, than for participants that never used statins.

Abbreviations as in Table 1.

1) continuous statin use over 6 years and to 2) users of individual statins. A further mixed model analysis was performed testing association between statin initiation and change in memory and global cognition. This analysis included 2 additional fixed effects: statin initiation (to test whether initiating statin therapy shifted cognitive level at the subsequent wave) and number of years since statin initiation (to examine whether beginning statin use altered the trajectory of cognitive change) (54).

The next set of analyses examined whether dementia risk factors moderated associations between statin ever use and memory and global cognition at baseline and over 6 years. Separate mixed model analyses were conducted for each risk factor (full factorial models between statin use, risk factor, and wave). The 2-way interactions in each model between the risk factor and statin ever use were examined for moderating associations with baseline memory and global cognition. Group differences in baseline performance may reflect that statin users with a dementia risk factor are on a different cognitive trajectory when entering observation (compared with statin never users or statin users without the risk factor). Three-way interactions between risk factor, statin ever use, and study wave, tested whether each risk factor moderated the association between statin ever use and changes in memory and global cognition over time. Statin ever use, wave, the dementia risk factor, and all 2- and 3-way interactions involving these variables were included as fixed effects in each model.

In the final set of analyses, the associations among statin ever use and baseline brain volumes and change over time were examined using linear mixed models. Random effects were included for both the intercept and wave. Statin ever use, wave, and the 2-way interaction between statin ever use and wave were included as fixed effects in each model. For completion, data are also presented for cerebrospinal fluid.

For exploratory purposes, we repeated the preceding analyses comparing groups on specific memory tests and tests evaluating other cognitive domains.

Across all linear mixed models, the following covariates were included: model 1 included sex, age, years of education, plus baseline intracranial volume in brain volume analyses; model 2 also included non-English-speaking background, BMI, heart disease, diabetes, stroke, hypertension, systolic blood pressure, smoking, and APOEε4 genotype carriage. The covariates heart disease, diabetes, stroke, hypertension, smoking, and APOE ε4 carriage were coded as binary variables with 1 and 0 representing the presence and absence of each risk factor, respectively. Model 2 was set as the final model for all outcome variables.

To examine the possibility of selective attrition, we compared the age and sex distribution, covariate prevalence, and baseline cognitive performance among participants with and without data on the final wave.

Analyses were performed using IBM SPSS Statistics version 23 (IBM Corp., Armonk, New York) (55). Considerations were made for multiple comparisons, and α value was adjusted using the Bonferroni method. For analyses of memory and global cognition, $p < 0.025$ was considered significant. For the main analyses of brain volumes (3 brain regions), $p < 0.016$ was considered significant. For exploratory analyses of specific memory test scores, $p < 0.01$ was considered significant.

RESULTS

BASELINE PARTICIPANT CHARACTERISTICS FOR STATIN EVER USERS AND NEVER USERS. Table 1 shows baseline demographic, metabolic, and cognition data for 1,037 participants stratified by statin ever use and never use. Most participants were Caucasian (98%) and Australian-born (67%) or European-born (18%). Mean education was 11.8 years (3 to 24 years). There were 395 statin never users, with 642 statin ever users (baseline ever users or commenced during observation), with a similar sex distribution between groups. The mean duration of statin use at baseline was 9.1 ± 6.9 years. A small number of participants used ezetimibe only (n = 10), fibrate only (n = 1), statin plus ezetimibe or fibrate (n = 42), or statin alternating with ezetimibe (n = 8).

At baseline, statin ever users were slightly younger, had higher BMI, and lower diastolic blood pressure than did never users. Over the observation period, 68% of statin users were continuous users.

As expected, statin ever users had higher prevalence of heart disease, diabetes, stroke, and hypertension (Table 1). Statin ever users had lower total, low-density, and high-density lipoprotein cholesterol levels and significantly higher fasting glucose, triglycerides, and insulin levels. Unadjusted baseline memory, global cognition, specific memory test performance, and other cognitive domains were similar between statin users and never users.

Raw data for all baseline cognition tests are shown in Online Table 1. Complete data were available for 573 participants (55.3%) over the 6 years. Participants with missing data (n = 464) were older (80.3 ± 5.0 years vs. 77.8 ± 4.4 years; $p < 0.001$), had slightly less education (11.2 ± 3.3 years vs. 11.9 ± 3.6 years; $p = 0.001$), were more likely to be from a non-English-speaking background (odds ratio [OR]: 1.60; $p = 0.008$), have heart disease (OR: 1.50; $p = 0.001$), never used statins (OR: 0.70; $p = 0.001$), and had lower baseline cognitive scores (all $p < 0.01$) (data not shown).

STATIN EVER USE, MEMORY, AND GLOBAL COGNITION. Table 2 shows the linear mixed model analyses results. For brevity, all results discussed refer to model 2, which adjusted for all covariates. A number of results were significant at a test-wise α value of 0.05, but not following Bonferroni correction. We have nonetheless elected to describe these results, explicitly noting test-wise, as opposed to statistical, significance.

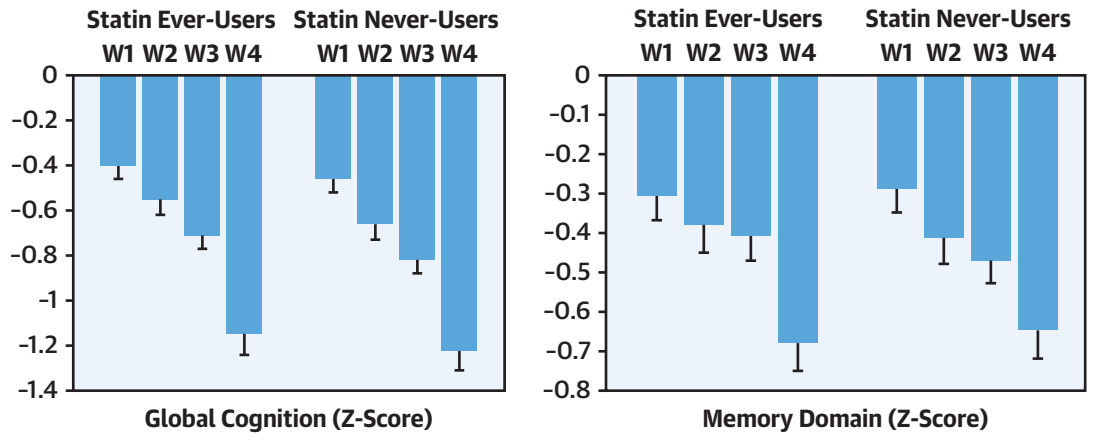
At baseline, statin ever users were similar to never users for memory and global cognition, as well as for the specific memory tests. Over 6 years of observation, there was no significant difference between statin ever users and never users for the rate of decline in memory and global cognition (Central Illustration), nor for specific memory test scores.

CONTINUOUS STATIN USE OVER 6 YEARS, MEMORY, AND GLOBAL COGNITION. At baseline, compared with never users, participants taking statins continuously over the 6-year observation period had statistically significantly higher baseline performance in memory and global cognition. Over 6 years of observation, the rate of decline in memory and global cognition was similar between continuous statin users and never users (Table 2).

STATIN TYPE, MEMORY, AND GLOBAL COGNITION. Statin type subgroups (simvastatin, atorvastatin, and pravastatin) were each compared with the group of statin never users. There were no significant differences between each subgroup and never users for baseline performance or rates of decline in memory and global cognition over 6 years (Table 2).

STATIN INITIATION, MEMORY, AND GLOBAL COGNITION. Statin therapy was initiated in 99 participants during observation; these participants were compared with

CENTRAL ILLUSTRATION **Statin Use, Global Cognition, and Memory**



Samaras, K. et al. J Am Coll Cardiol. 2019;74(21):2554–68.

Global cognition and memory domain scores in statin ever users and never users in the MAS (Sydney Memory and Ageing Study). Data shown are mean ± SEM domain scores for global cognition and memory at baseline and at 2 yearly assessments for participants who underwent all 4 waves (W) of assessments over the 6 years of observation (n = 402 statin ever users and n = 206 statin never users).

never users. At the test-wise significance level, the initiation of statin therapy was associated with an attenuation in the rate of decline of memory over subsequent measures (B = 0.066; p = 0.038). Statin initiation was not associated with a shift in global cognition performance or rate of decline at subsequent waves (**Table 2**).

Exploratory analyses of specific memory tests (**Table 2**) and other cognitive domains (Online Table 2) found no differences in baseline performance and rates of decline between statin never users and each of ever users, continuous users, and specific statin types. Exploratory analyses of specific memory tests found that statin initiation was associated with attenuation in the rate of decline of long-delayed recall (RAVLT-7) over subsequent measures, compared with statin never users (B = 0.092; p = 0.002) (**Table 2**), which remained significant after Bonferroni correction. No significant results emerged in the exploratory analyses of non-memory domains and statin initiation (Online Table 2).

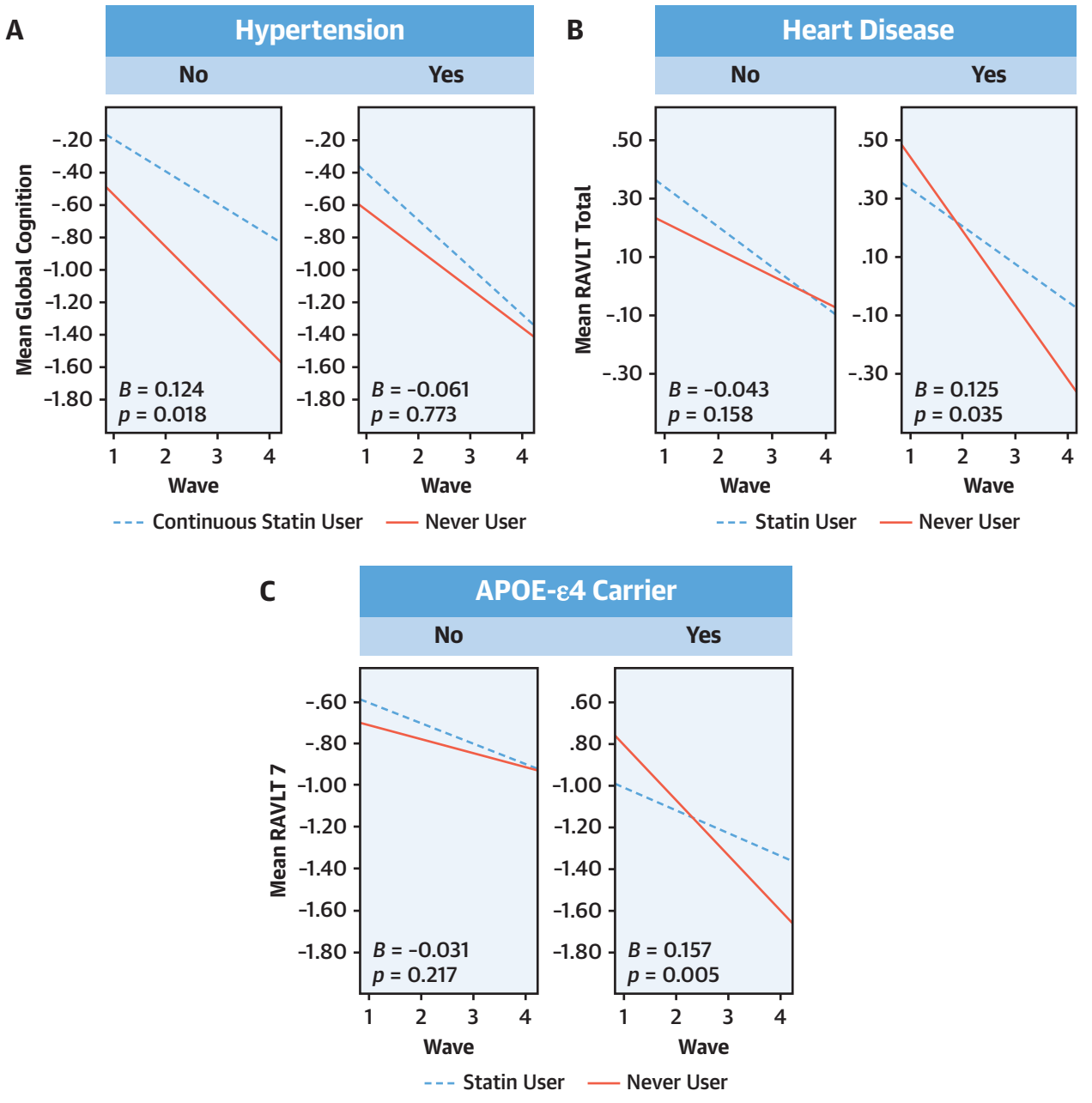
INTERACTIONS BETWEEN DEMENTIA RISK FACTORS AND STATIN EVER USE. Associations with baseline memory and global cognition. Associations between statin-use categories and cognition and at baseline and after 6 years' observation were sought. None were found (Online Table 3).

The 2-way interactions between statin use and each risk factor were then examined to identify whether the relationship between each risk factor and baseline memory and global cognition differed between statin ever users and never users. No significant interactions were found between statin ever use and any dementia risk factor for baseline memory or global cognition (Online Table 4).

In analyses limited to continuous statin users compared with never users, no interactions were found among continuous statin use, baseline memory scores, or baseline global cognition (Online Table 5).

ASSOCIATIONS WITH CHANGES IN MEMORY AND GLOBAL COGNITION OVER 6 YEARS. Three-way interactions among statin ever use, risk factors, and wave were interrogated to identify whether statin ever use moderated the relationship between each risk factor and decline in memory and global cognition. None emerged as significant following Bonferroni adjustment (Online Table 4). At the test-wise level of significance, statin ever use moderated the relationship between hypertension and decline in global cognition over 6 years (model 2: B = −0.128; p = 0.048). When the analysis was limited to continuous statin users compared with never users, the interaction was larger and significant (B = 0.173; p = 0.013) (Online Table 5). **Figure 1A** shows that in normotensive participants, continuous statin users displayed significantly slower decline in global cognition (B = 0.124; p = 0.018), whereas this difference was not significant in hypertensive participants (B = −0.061; p = 0.773).

FIGURE 1 **Interactions Between Dementia Risk Factors, Cognition, and Statin Use in Hypertension, Heart Disease, and APOEε4 Genotype**



Data from the MAS (Sydney Memory and Ageing Study) are fitted trajectories showing changes over time on selected cognitive outcome variables for statin ever users compared with statin never users **(A)** with and without hypertension, **(B)** with and without heart disease, and **(C)** who are carriers and noncarriers of the apolipoprotein Eε4 (APOEε4) genotype. RAVLT7 = Rey Auditory Verbal Learning Test–long-delayed recall; RAVLT Total = Rey Auditory Verbal Learning Test–total learning.

Exploratory analyses of specific memory tests found test-wise significant interactions between statin ever use and the following: 1) heart disease on decline in total learning (RAVLT-total: B = 0.169; p = 0.013); 2) ApoEε4 on the decline in long-delayed recall (RAVLT-7: B = 0.188; p = 0.003); and 3) sex on the decline in logical memory (B = 0.146; p = 0.013).

First, a protective interaction was found among statin ever use, heart disease, and the 6-year change in RAVLT-total score. As shown in **Figure 1B**, among

TABLE 3 Associations of Statin Use With Brain Volumes: Baseline and Changes in Brain Volume Over 2 Years

	Model 1*						Model 2†					
	Baseline			Volume Decline Over 6 yrs			Baseline			Volume Decline Over 6 yrs		
Group Comparison‡	B§	SE	p Value	B‖	SE	p Value	B§	SE	p Value	B‖	SE	p Value
Statin ever users vs. never users												
Total brain volume, mm^3	−0.134	0.069	0.05	−0.004	0.048	0.94	−0.040	0.061	0.51	−0.013	0.051	0.80
Hippocampus, mm^3	−0.058	0.062	0.35	−0.050	0.078	0.53	−0.009	0.061	0.89	−0.038	0.086	0.66
Parahippocampus, mm^3	−0.024	0.068	0.72	−0.090	0.072	0.21	0.047	0.068	0.49	−0.090	0.078	0.25
Cerebrospinal fluid, mm^3	−0.046	0.081	0.57	0.032	0.077	0.68	0.031	0.051	0.55	0.001	0.082	0.99
Continuous statin users vs. never users												
Total brain volume, mm^3	−0.057	0.056	0.31	−0.021	0.045	0.67	−0.021	0.062	0.73	−0.026	0.051	0.61
Hippocampus, mm^3	0.014	0.056	0.80	−0.016	0.083	0.85	−0.014	0.061	0.82	−0.015	0.087	0.87
Parahippocampus, mm^3	0.023	0.062	0.71	−0.081	0.075	0.29	0.041	0.068	0.55	−0.082	0.079	0.30
Cerebrospinal fluid, mm^3	0.043	0.047	0.36	0.020	0.079	0.80	−0.015	0.051	0.79	0.018	0.083	0.82

B is the regression coefficient. SE is the standard error of B. The p value is the level of statistical significance for the rejection of the null hypothesis B = 0. *Model 1's covariates include age, sex, education, and baseline intracranial volume. †Model 2's covariates include age, sex, education, non-English-speaking background, body mass index, ever smoker, heart disease, diabetes, stroke, hypertension, systolic blood pressure, and baseline intracranial volume. ‡Sample sizes for the groups in each comparison are as follows. For unadjusted analyses (i.e., model 1): statin ever users n = 332, never users n = 197; all lipid-lowering medication ever users n = 335, never users = 194; continuous statin users n = 215, never users = 196; for adjusted analyses (i.e., model 2): statin-ever users n = 307, never users n = 186; all lipid-lowering medication ever users n = 309, never users n = 184; continuous statin users n = 108, never users n = 186. §Regression coefficient reflects the mean difference in standardized brain volume units at baseline between the groups being compared, adjusting for the covariates specified for that model. Positive values indicate the first group in the comparison had better average baseline performance than the second (i.e., reference) group. ‖Regression coefficient reflects the difference between groups in their average change in brain volume per year, in standardized units, adjusting for the covariates specified for that model. Positive values indicate that the first group in the comparison had a slower rate of decline in brain volume per year compared to the second (i.e., reference) group.

participants with heart disease, statin ever users, compared with never users, displayed a slower rate of decline in RAVLT-total, which was significant at the test-wise level (B = 0.125; p = 0.036). In participants without heart disease, there was a comparable rate of decline in RAVLT-total scores between statin ever users and never users (B = 0.044; p = 0.173). This interaction was also found in analyses limited to continuous statin users compared with never users (p = 0.044) (Online Table 5).

Similarly, a protective interaction was found among ApoEε4 carriage, statin ever use, and the rate of decline in long-delayed recall (RAVLT-7) performance (**Figure 1C**). In ApoEε4 carriers, statin ever use was associated with a significantly slower rate of decline over 6 years compared with the rate of decline in never users (B = 0.157; p = 0.005); in noncarriers the rate of decline in long-delayed recall performance was similar between statin ever users and never users (B = −0.031; p = 0.320). This interaction was also found in analyses limited to continuous statin users compared with never users (p = 0.003) (Online Table 5).

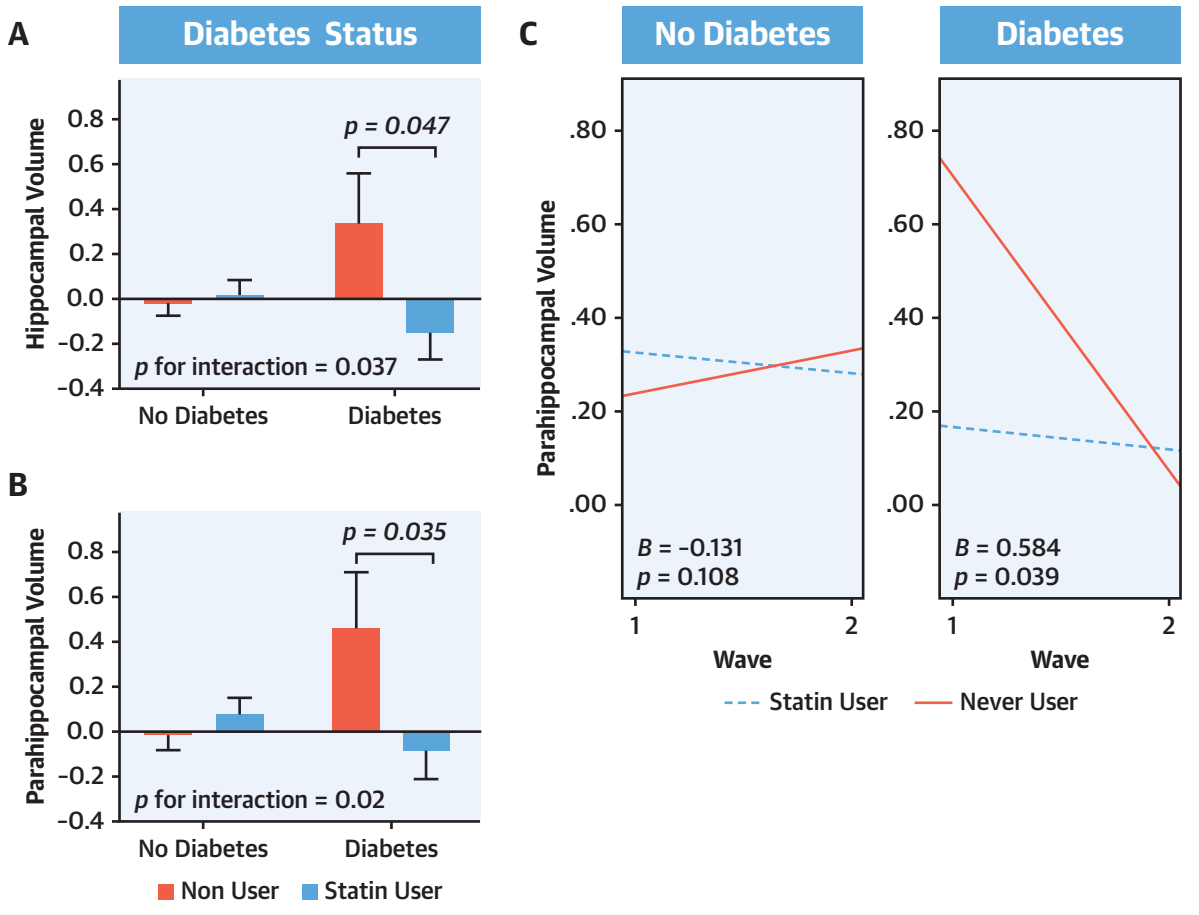
Finally, there was a test-wise statistically significant interaction between sex and statin ever use (B = 0.146; p = 0.013). Male statin users displayed significantly faster logical memory decline than did male never users (B = −0.101; p = 0.020), whereas decline between statin ever users and never users was comparable in female subjects (B = 0.045; p = 0.250).

For completion, Online Table 5 presents the results of risk factor interaction analyses for continuous statin use and changes in memory, global cognition, and specific memory tests and for statin ever use and changes in other cognitive domains (Online Table 6).

STATIN EVER USE AND BRAIN VOLUME CHANGES OVER 2 YEARS. Statin ever users and never users had similar total brain volume, hippocampal and parahippocampal brain volumes at baseline, adjusted for the covariates of age, heart disease, diabetes, stroke, systolic blood pressure, BMI, and baseline intracranial volume. There were no significant differences in the changes in these brain volumes over 2 years. Similar null results were found when examining continuous statin use compared with never use (**Table 3**).

DEMENTIA RISK FACTORS, STATIN EVER USE, AND BRAIN VOLUME CHANGE OVER 2 YEARS. We first examined the 2-way interactions between each dementia risk factor on baseline brain volumes. Test-wise significant interactions were only found for the risk factor of diabetes, which moderated associations between statin ever use and baseline hippocampal (p = 0.037) and parahippocampal volumes (p = 0.020) (**Figures 2A and 2B**). In participants with diabetes, statin ever users had lower baseline hippocampal (B = −0.479; p = 0.041) and parahippocampal volumes (B = −0.541; p = 0.035) than did never users, with both differences significant at the test-wise level

FIGURE 2 Interactions Between Diabetes, Hippocampal and Parahippocampal Volumes, and Statin Use



The MAS (Sydney Memory and Ageing Study) data shown are hippocampal **(A)** and parahippocampal **(B)** volume (mean ± SD) and **(C)** 2-year rates of change in parahippocampal volume for statin ever users and never users with and without diabetes.

only. In contrast in participants without diabetes, baseline hippocampal (B = 0.026; p = 0.667) and parahippocampal (B = 0.085; p = 0.219) volumes were similar in statin ever users and never users (Table 4). Similar results were evident in analyses limited to continuous statin users compared with statin never users (Online Table 7).

Three-way interactions were next examined among statin ever use, dementia risk factors, and the change in brain volumes over 2 years. A statistically significant interaction was found for diabetes, indicating that diabetes moderated the relationship between statin use and change in parahippocampal volume over 2 years (p = 0.016). As shown in Figure 2C, among participants without diabetes, statin ever users and never users displayed comparable rates of change in parahippocampal volume (B = −0.131; p = 0.108); in contrast, among participants with diabetes, statin ever users had a significantly slower rate of decline in parahippocampal volume than did statin never users, which was significant at the test-wise level (B = 0.584; p = 0.039).

DISCUSSION

This study examined statin use, global cognition, and changes in memory and global cognition over 6 years and brain volumes over 2 years in community-dwelling elderly Australians. To our knowledge, this is the longest observational cohort study reporting memory and statin use in the elderly population. Using the best statistical models available currently, we interrogated the widely held consumer concern

TABLE 4 Interaction Between Statin Ever Use, Risk Factors, and Brain Volumes: Associations With Baseline and Change Over 2 Years

	Model 1*						Model 2†					
	Baseline Statin Users vs. Never Users			Volume Decline Over 6 yrs Statin Users vs. Never Users			Baseline Statin Users vs. Never Users			Volume Decline Over 6 yrs Statin Users vs. Never Users		
	B‡	SE	p Value	B§	SE	p Value	B‡	SE	p Value	B§	SE	p Value
Heart disease												
Total brain volume, mm^3	−0.037	0.150	0.81	0.007	0.132	0.96	0.037	0.152	0.81	−0.019	0.137	0.89
Hippocampus, mm^3	−0.098	0.150	0.52	0.053	0.222	0.81	−0.034	0.151	0.82	0.083	0.232	0.72
Parahippocampus, mm^3	0.131	0.166	0.43	−0.027	0.201	0.89	0.214	0.168	0.20	0.022	0.211	0.92
Cerebrospinal fluid, mm^3	0.018	0.126	0.89	0.006	0.212	0.98	−0.049	0.127	0.70	0.000	0.222	1.000
Type 2 diabetes												
Total brain volume, mm^3	0.168	0.232	0.47	0.148	0.189	0.43	0.164	0.243	0.50	0.133	0.192	0.49
Hippocampus, mm^3	−0.450	0.230	0.05	0.605	0.318	0.06	−0.505	0.241	0.037	0.604	0.326	0.06
Parahippocampus, mm^3	−0.529	0.255	0.038	0.703	0.287	0.015	−0.626	0.267	0.02	0.715	0.294	0.016
Cerebrospinal fluid, mm^3	−0.124	0.195	0.52	−0.294	0.305	0.34	−0.127	0.204	0.53	−0.278	0.313	0.38
Stroke												
Total brain volume, mm^3	−0.366	0.480	0.45	0.281	0.358	0.43	−0.360	0.481	0.46	0.268	0.361	0.46
Hippocampus, mm^3	−0.425	0.485	0.38	−0.499	0.604	0.41	−0.348	0.478	0.47	−0.501	0.611	0.41
Parahippocampus, mm^3	−0.775	0.536	0.15	0.247	0.545	0.65	−0.794	0.530	0.14	0.241	0.553	0.66
Cerebrospinal fluid, mm^3	0.263	0.403	0.51	0.431	0.582	0.46	0.255	0.403	0.53	0.474	0.590	0.42
Hypertension												
Total brain volume, mm^3	0.096	0.113	0.40	0.021	0.100	0.84	0.035	0.116	0.76	0.022	0.103	0.83
Hippocampus, mm^3	0.173	0.113	0.13	0.091	0.168	0.59	0.152	0.115	0.19	0.054	0.175	0.76
Parahippocampus, mm^3	0.203	0.125	0.11	0.027	0.152	0.89	0.187	0.127	0.14	−0.004	0.159	0.98
Cerebrospinal fluid, mm^3	−0.086	0.095	0.37	0.247	0.160	0.12	−0.039	0.097	0.69	0.242	0.167	0.15
Smoking												
Total brain volume, mm^3	−0.029	0.112	0.80	0.071	0.099	0.47	−0.103	0.115	0.37	0.079	0.102	0.44
Hippocampus, mm^3	−0.012	0.113	0.91	0.004	0.164	0.98	−0.025	0.115	0.83	−0.011	0.171	0.95
Parahippocampus, mm^3	−0.063	0.125	0.62	0.036	0.149	0.81	−0.084	0.127	0.51	0.023	0.155	0.89
Cerebrospinal fluid, mm^3	0.006	0.094	0.95	0.031	0.159	0.84	0.066	0.096	0.50	0.029	0.166	0.86
Sex												
Total brain volume, mm^3	0.090	0.112	0.42	0.003	0.098	0.97	−0.009	0.115	0.94	0.021	0.102	0.84
Hippocampus, mm^3	0.059	0.112	0.60	0.081	0.166	0.63	−0.022	0.114	0.85	0.039	0.173	0.82
Parahippocampus, mm^3	0.018	0.124	0.88	0.095	0.151	0.53	−0.091	0.127	0.47	0.077	0.157	0.63
Cerebrospinal fluid, mm^3	−0.077	0.094	0.41	0.205	0.157	0.19	0.009	0.096	0.93	0.187	0.164	0.26
Age at baseline												
Total brain volume, mm^3	0.018	0.119	0.88	0.075	0.105	0.47	0.071	0.122	0.56	0.076	0.109	0.49
Hippocampus, mm^3	−0.061	0.117	0.60	−0.123	0.175	0.48	−0.045	0.120	0.71	−0.128	0.184	0.49
Parahippocampus, mm^3	−0.011	0.129	0.93	−0.055	0.160	0.73	−0.015	0.132	0.91	−0.081	0.168	0.63
Cerebrospinal fluid, mm^3	−0.016	0.099	0.88	0.123	0.169	0.47	−0.061	0.102	0.55	0.127	0.178	0.48

B is the regression coefficient. SE is the standard error of B. The p value is the level of statistical significance for the rejection of the null hypothesis B = 0. *Model 1's covariates include age, sex, education, and baseline intracranial volume. †Model 2's covariates include age, sex, education, non-English-speaking background, body mass index, ever smoker, heart disease, diabetes, stroke, hypertension, systolic blood pressure, and baseline intracranial volume (unless examined as a risk factor). ‡Regression coefficients represent the difference in the association between statin use and baseline brain volume (in standardized units) between those with versus without the specified risk factor. §Regression coefficients represent the difference in the association between statin use and annual rate of decline in brain volume between those with versus without the specified risk factor.

that statin medications are associated with adverse memory effects. Our analyses did not find any supporting evidence for such a concern, examining memory as a composite domain score derived from a battery of memory performance tests, as well as by individual test performance (**Central Illustration**). Furthermore, there was no evidence that statin use was associated with greater decline in global cognition or in other cognitive domains. Our results were consistent when data were examined as statin ever use or continuous statin use over 6 years.

Interestingly an association was found between statin initiation during observation and blunting in the rate of decline in memory after at least 2 years. This may represent a benefit of commencing statin therapy in the elderly population, or it may be attributed to selection or prescription biases: participants age 70 to 90+ years who are prescribed statin therapy may be on a better memory trajectory from those who are not. No association was found between statin use and brain volume changes over 2 years. Importantly this study is among a few to

comprehensively control for the potential impact of important covariates that influence cognitive decline in the elderly population, not limited to heart disease, diabetes, stroke, hypertension, age, sex, smoking, education, obesity, and dementia genetic susceptibility.

Furthermore, to examine the possibility that statins may unmask memory difficulties in those predisposed to cognitive impairment or dementia, interactions were sought between statins, dementia risk factors, and memory and global cognition change over 6 years. None were found for the primary analyses of memory domain or global cognition. In secondary exploratory analyses interrogating specific memory tests, we found protective interactions between statin ever use and (separately) heart disease and ApoEε4 genotype: statin ever users had slower rates of decline in specific memory test performance over 6 years in the presence of these risk factors. Statin users with heart disease had a significantly slower decline in total learning (RAVLT-total). Statin users with the ApoEε4 dementia predisposition genotype had significantly slower decline in long-delayed recall (RAVLT-7). APOEε4 has been implicated as exacerbating the vascular component of dementia in patients with Alzheimer degenerative dementia by increasing small-vessel vascular resistance; statins may mitigate this mechanism. These results were confirmed in analyses limited to continuous users of statin medications over the observation. A third interaction was found between the statin users with diabetes, with attenuated rate of decline in parahippocampal volume. As these analyses were exploratory and not corrected for multiple comparisons, no firm conclusions should be drawn.

The findings from our observational study are in accord with randomized (6,7,17,29-31) and observational (15-18,24) studies.

Strengths of the current study include detailed assessment of memory using 5 different tests, each examining different aspects of memory; repeated testing on 4 occasions during the 6-year observation period; the large cohort size; and the performance of magnetic resonance brain imaging with specific volumetric assessment of brain regions considered important to memory in a large subgroup. Strengths in the analytical design include use of linear mixed modeling to address, as best as can be statistically, the bias introduced by dropouts. To date, this is the first cohort study to use this statistical technique. Additional statistical strengths were the inclusion of important covariates influencing brain aging, detailed interrogation of different levels of statin exposure, and examination for interactions with dementia risk factors.

STUDY LIMITATIONS. Study limitations include the observational study design and the potential for selection bias and survivor bias to influence results, despite the modeling approaches undertaken. There were baseline differences between the groups for dementia risk factors and lower cognition in dropouts. As much as is statistically possible, both were addressed by controlling for important covariates as far as possible and using minimal modelling, to our knowledge more so than any other observational study or trial has done to date in this area. Finally, participants with Mini Mental State Examination scores <24 were excluded; therefore, no conclusions can be made for those with more advanced cognitive impairment.

CONCLUSIONS

Statin use in the elderly population was not associated with any acceleration in decline in memory, global cognition, or brain volumes in community-dwelling elderly Australians. Protective associations were found for some aspects of memory testing in those with dementia risk factors such as heart disease and ApoEε4 gene carriage. This study offers reassurance to consumers who hold concerns about harmful statin effects on memory and cognition.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Over a period of 6 years, statin therapy has no consistent adverse impact on memory or cognitive function in elderly patients.

TRANSLATIONAL OUTLOOK: Prospective studies are needed to exclude differential effects of statin therapy on cognitive function in patients with risk factors for various specific forms of dementia.

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APPENDIX For supplemental tables, please see the online version of this paper.