RESEARCH REPORT

Statins and serum cholesterol's associations with incident dementia and mild cognitive impairment

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► An additional appendix is published online only. To view this files please visit the journal online (http://jech.bmj.com).

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MAB had full access to the data used in this manuscript and completed all the statistical analyses.

Accepted 15 April 2010
Published Online First 14 September 2010

ABSTRACT

Background Statin use and serum cholesterol reduction have been proposed as preventions for dementia and mild cognitive impairment (MCI).

Methods 1604 and 1345 eligible participants from the Baltimore Longitudinal Study of Aging (BLSA) were followed after age 50 for a median time of around 25 years, to examine the incidence of dementia (n=259) and MCI (n=138), respectively. Statin use (ever-use and time-dependent use), total cholesterol levels (TC; first visit and time-dependent), TC change trajectory from first visit and high-density lipoprotein (HDL-C):TC ratio (first visit and time-dependent) were the main exposures of interest. Cox proportional hazards models were used.

Results Participants with incident dementia had a higher first-visit TC compared with participants who remained free of dementia and MCI, while first-visit TC was higher among statin ever-users compared with never-users (age-unadjusted associations). Statin users had a two- to threefold lower risk of developing dementia (HR=0.41; 95% CI 0.18 to 0.92), but not MCI, when considering time-dependent 'statin use' with propensity score model adjustment. This association remained significant independently of serum cholesterol exposures. An elevated first-visit TC was associated with reduced MCI risk (upper quartile (Q_4) vs Q_1: HR=0.51; 95% CI 0.29 to 0.90). Compared with the lowest quartile (Q_1: 0.00–0.19), HDL-C:TC (time-dependent) in (Q_2: 0.19–0.24) was associated with reduced MCI risk (HR=0.58; 95% CI 0.34 to 0.98). Among men only, TC decline from first visit was significantly associated with increased dementia risk (HR=4.21; 95% CI 1.28 to 13.85).

Conclusions Statins may have multifactorial effects on dementia but not MCI risk. Future interventions may be warranted, and research should focus on optimal serum TC, HDL-C:TC ratio and TC change trajectories.

INTRODUCTION

Statins have been proposed as agents for preventing dementia and other neurological disorders,[1–7] though a recent meta-analysis of prospective cohort and case–control studies suggested that statins are less beneficial in reducing dementia risk than expected.[8] More recent cohort studies conducted since this meta-analysis suggested that statins may have a protective effect against incidence of dementia, mild cognitive impairment (MCI) and Alzheimer's disease or their combination,[9–11] although at least one other study did not find any association.[12]

The direct effects of plasma total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-C) and high-density lipoprotein-cholesterol (HDL-C) on the incidence of dementia and cognitive decline are controversial, based on recent epidemiological evidence.[13–18] Due to the potential multifactorial actions of statins,[19] it is biologically plausible that statin therapy may reduce risk of dementia and even delay onset of MCI, independently of the effects of statin on serum cholesterol.

We analysed data from a large prospective study with median follow-up time of over 20 years. Our main study aims were to examine (1) the association of statin use with incidence of dementia and MCI, and whether it is altered by serum cholesterol levels; (2) the putative independent effect of first-visit or time-dependent serum TC and TC changes on incidence of dementia and MCI; and (3) the influence of first-visit and time-dependent HDL-C:TC ratio on dementia and MCI risks.

METHODS

Study design and participants

We used data from the Baltimore Longitudinal Study of Aging (BLSA), an ongoing prospective study of community-dwelling adults.[20] BLSA participants were initially recruited in 1958, new participants were continuously enrolled since then, and most participants had at least one follow-up interview after a 1–2-year interval, though frequency of follow-up and interwave period varied for each BLSA participant. In our present analysis, with dates of visits ranging between 6 February 1958 and 3 August 2006, about 75% of the total sample (n=3005) had two visits or more. Participants became at risk at age 50 years and exited follow-up at first failure, defined as incident MCI or dementia at or beyond age 50 years or when censored at last examination visit (end of follow-up), or due to death or loss to follow-up. Of the original sample (n=3005 BLSA participants, age range: 17–97 at first visit; 60.1% men), 2322 were at risk of dementia or MCI, given that they had at least one visit ≥50 years of age. As both statin use and case conferencing were initiated in the mid-1980s, participants having all visits prior to 1985 were excluded from this study (n=392), leaving 1930 eligible subjects. Participants with unknown outcomes by the end of follow-up (n=326 out of 1930) were also excluded, resulting in 1604 eligible participants in our final analysis with dementia as the main outcome. In analyses in which MCI was the main outcome, participants with incident

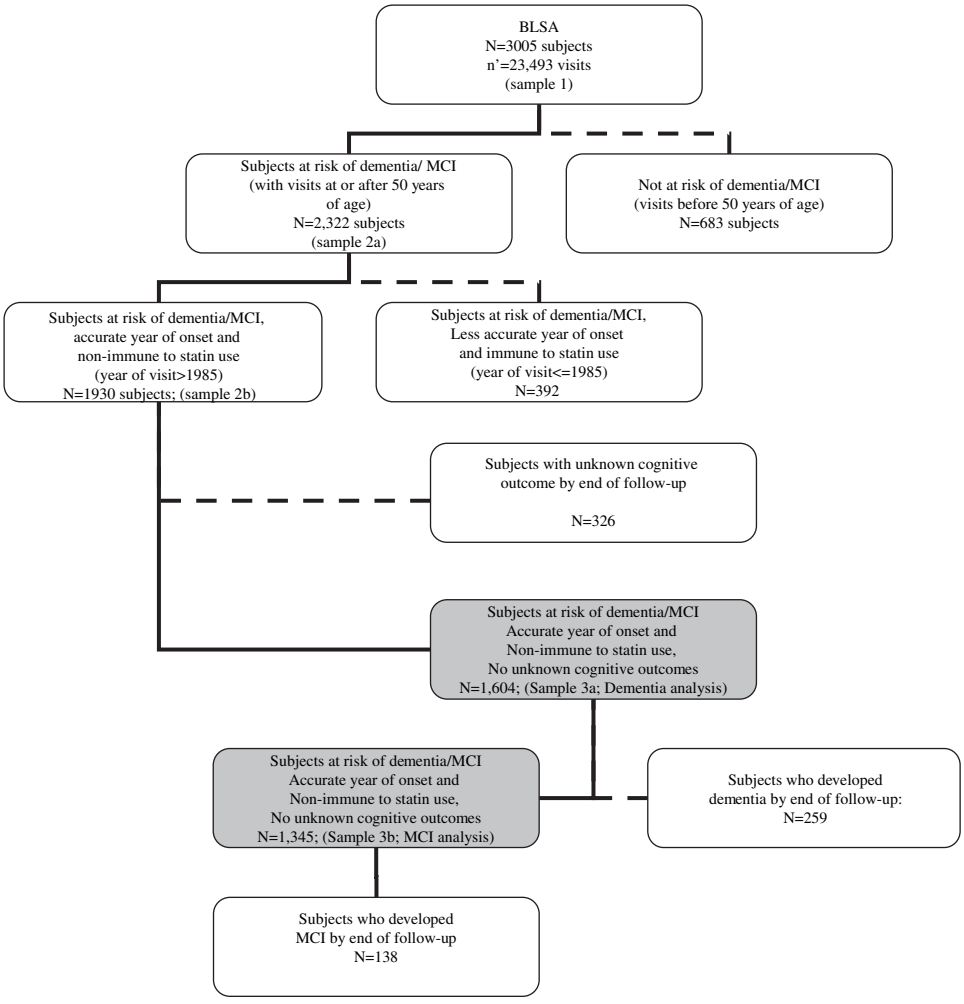

Figure 1 Diagram for inclusion and exclusion of Baltimore Longitudinal Study on Aging (BLSA) participants into main analyses. Sample 1 was used for prediction of total cholesterol trajectories with linear mixed models; Sample 3 was used for fitting Cox proportional hazard models and running Kaplan–Meier survival curves. 'Subjects immune to statin use' are those with visits that preceded the introduction of statins into the market (ie, prior to 1985). 'Subjects with less accurate year of onset' are those whose diagnosis of dementia or mild cognitive impairment (MCI) was done retrospectively since case conferencing was initiated in the mid-1980s.

dementia during follow-up were excluded, leaving 1345 at risk for MCI (figure 1). The protocol of the BLSA was reviewed by the Institutional Review Board on Human Subjects at the National Institute on Aging, Intramural Research Program.

Incident dementia and MCI

All participants were followed up every 1–2 years depending on age and were reviewed at a consensus conference if their Blessed Information-Memory-Concentration score[21] was ≥4, if their informant or subject Clinical Dementia Rating (CDR)[22] score was ≥0.5 or if their Dementia Questionnaire (DQ)[23] was abnormal.

Dementia diagnosis was determined at a consensus conference based on criteria from the DSM-III-R[24] and from the National Institute of Neurological and Communication Disorders—Alzheimer's Disease and Related Disorders Association.[25] Diagnosis required evidence of a progressive cognitive syndrome, including memory decline and functional loss based on self-reported and informant-reported Clinical Dementia Ratings.[22 26 27] The method of diagnosis has been detailed and validated elsewhere.[28]

A diagnosis of MCI not meeting criteria for dementia was made following the Petersen criteria[29] when participants had either single domain cognitive impairment (usually memory) or cognitive impairment in multiple domains without significant functional loss in activities of daily living (ADL; assessed with the CDR and Pfeffer Functional Activities Questionnaire). Cases of MCI were retained in the 'at risk for dementia' group. The year of onset for MCI was estimated using the same methodology as for dementia. In our present analysis, incident MCI was considered as one of the main outcomes of interest. Among the population at risk of developing either MCI or dementia, those who developed dementia by the end of follow-up were removed from this analysis at the beginning of follow-up, leaving the contrast between MCI and the non-demented group.

Statin use

A detailed inventory of all over-the-counter and prescription medications in current use were obtained at each visit. Participants using lovastatin, simvastatin, cerivastatin, atorvastatin, pravastatin or fluvastatin were considered as having used statins at a particular visit. Two exposure variables were constructed to examine effect of statin use on MCI and dementia risk, alternatively.

- Definition 1 (ever-use of statins, time-independent): A person is exposed if they ever-used statins beyond age 50 years but prior to incidence of the dementia or MCI outcomes or censoring at end of follow-up. Eligible participants are considered unexposed if they never-used statins (n=1486) or if they used them only at or prior to age 50 (n=3) or only at or after onset of dementia or MCI (n=5).
- Definition 2 (time-dependent use of statins): A person is considered a user at first use and afterwards as long as they were free of outcome at that point in time and as long as statins are used beyond 50 years of age.

Serum cholesterol exposures

Antecubital venous blood samples were drawn following an overnight fast and used to determine plasma lipid levels. TC (mg/dl) was determined by enzymatic methods (Abbott Laboratories ABA-200 ATC Biochromatic Analyzer, Irving, Texas). HDL-C concentration (mg/dl) was assessed by dextran sulfate–magnesium precipitation procedures.[30] Measurements on TC and HDL-C were carried out at different times for each participant. TC and the HDL-C:TC ratio were examined at first visit (ie, visit 1) as well as time-dependent variables. In the latter, missing values were imputed with values of TC or HDL-C in the preceding non-missing visit, using Stata's stfill command with forward option.[31] Analysis was conducted using quartiles of cholesterol exposures, which were classified as such based on available data for eligible participants at first visit ('time-independent' approach) or over the follow-up period ('time-dependent' approach). Moreover, TC change trajectory between first visit and age 50 (when follow-up started for dementia and MCI risk started) was also considered. To this end, a multivariable linear mixed model was carried out, and empirical Bayes estimator of slope (annual rate of change) at first-visit age was predicted (see appendix 1 for more detail). The slope was then dichotomised in our final analyses as 'same or upward sloping' trajectory (when the annual rate of change was 0 or positive) and 'downward sloping' trajectory (when the annual rate of change was negative).

Covariates

Potentially confounding covariates were measured at first visit for eligible participants. Covariates included: (1) demographic and lifestyle factors such as age at first visit, sex, race and ethnicity, education (years of schooling) and smoking status (never, former or current smoker); (2) self-reported history of type 2 diabetes, hypertension, cardiovascular disease (CVD) (stroke, congestive heart failure, non-fatal myocardial infarction or atrial fibrillation) and dyslipidaemia; (3) directly measured metabolic outcome variables: body mass index (BMI=weight in kg over squared height in m^2), blood pressure (systolic and diastolic in mm Hg) and fasting blood glucose (in mg/dl). Due to appreciable missing data on many metabolic variables, only BMI and SBP were considered in the multivariable analyses as potential confounders.

Statistical analysis

All analyses were performed using Stata version 10.0 (Stata, College Station, Texas).[31] First, statin users were compared with non-users and dementia, and MCI cases were compared with non-cases, using ANOVA, t test and χ^2 tests. Second, to examine the associations between statin use and cholesterol exposures on the one hand and incidence of dementia or MCI on the other, survival analyses were conducted (see aims 1, 2 and 3 in Introduction). To this end, Kaplan–Meier survival curves and logrank tests were used to compare the number of incident dementia or MCI cases by exposure category. We further conducted Cox proportional hazards (PH) models to examine if dementia or MCI risks were associated with statin use (time-dependent), after adjusting for various socio-demographic, lifestyle and metabolic factors. Another set of analyses examined the effects of serum cholesterol on dementia and MCI risks, adjusting for statin use. In both analyses, the dependent variables were age at dementia or MCI onset or the last observed (censored) age of non-cases, adjusting for covariates (see Covariates section). A sensitivity analysis was conducted to account for confounding by indication.[32] In particular, we estimated probability of statin use from a multivariable logistic model in which socio-demographic, first-visit smoking status, metabolic factors (mainly BMI, SBP and DBP at first visit) and history of comorbid conditions (including dyslipidaemia and CVD) at first visit were included as predictors. This predicted probability, also known as the propensity score (PS),[33] was then grouped into quintiles and introduced into a Cox PH model where observed statin use was the only exposure variable predicting risk of dementia ('PS adjustment method'). Effect modification by sex was examined in part of the analysis. Type I error used for statistical significance was 0.05 for all analyses.

RESULTS

First-visit characteristics of the BLSA study sample

Of 1604 eligible participants at risk and after a median follow-up of 24.9 years, 259 participants developed dementia (70%; n=182 were AD). Among the population at risk excluding dementia cases that developed by the end of follow-up (n=259), 138 developed MCI after a median 25.1 years of follow-up. Statin ever-users (n=110) differed from statin never-users (n=1494) on most first-visit covariates, except for type 2 diabetes, hypertensive status, systolic and diastolic blood pressures (table 1). Compared with never-users, statin ever-users were older, had higher proportions women and minority ethnic groups, and were less likely to be current smokers. Ever-users also had a greater prevalence of CVD, dyslipidaemia ($p<0.05$ based on χ^2 test), and they had higher TC, lower HDL-C and higher glucose levels on average compared with non-users ($p<0.05$ based on two-sided t test). The lack of correspondence between statin ever-use and dyslipidaemia at first visit is due to the differences in the predefined time frames for the two variables. Comparing participants by dementia or MCI status, both MCI and dementia cases were older at first visit and less likely to be current smokers, and had a higher prevalence of self-reported hypertension at first visit ($p<0.05$ for χ^2 test) compared with non-cases (table 1). They also had higher mean levels of SBP and DBP ($p<0.05$ based on a two-sided t test with Bonferroni correction). Dementia cases, but not MCI cases, had a significantly higher TC compared with non-cases (229.4 vs 218.9, $p<0.05$ based on a two-sided t test with Bonferroni correction). However, dementia cases were the least likely to report having dyslipidaemia at first visit (0.8% vs 5.1% among MCI and 6.0% among non-cases, $p<0.05$ for χ^2 test). In fact, statin use was lowest among dementia cases, followed by MCI and was the highest among non-cases ($p<0.05$ for χ^2 test). Moreover, incident MCI cases had significantly higher glucose levels and lower HDL-C compared with non-cases ($p<0.05$ based on two-sided t test with Bonferroni correction). Statins used were mostly lipophilic, and the mean age at self-reported statin use (n=110) was 72.7 years with a SD=9.0, with a range of 51.2–92.4 years.

Statin use, dementia and MCI risk

Figure 2A shows Kaplan–Meier survival curves for incident dementia comparing 'statin ever-users' with 'statin never-users' (time-independent variable). The curves indicate that statin ever-users are at a reduced risk of developing dementia over time with a logrank test p value of 0.0002. Multivariable-adjusted Cox PH models yielded a HR, indicating that statin users were at around a fivefold lower risk of developing dementia compared with statin non-users (HR: 0.21; 95% CI 0.09 to 0.48). Substituting the statin ever-use exposure (definition 1) with the time-dependent definition of statin use (definition 2; see Methods) and combining it with the PS modelling approach yielded an HR of 0.41 with a 95% CI 0.18 to 0.92 (figure 3A).

Table 1 Characteristics of participants included in main analysis according to 'statin ever-use' (definition 1)¶ and dementia or mild cognitive impairment (MCI) status; Baltimore Longitudinal Study of Aging

	Statin ever-use, total¶				Dementia/MCI status			
	All	Statin never-user	Statin ever-user		No dementia or MCI	Incident dementia	Incident MCI	
N	1604	1494	110		1207	259	138	
Sex (percentage women)	38.5	37.7	49.1	†	39.6	36.3	33.3	
Race/ethnicity (%)								
NH white	91.4	91.8	86.4		89.8	97.1	95.7	†
NH black	7.3	7.0	10.9		8.6	2.5	4.3	
Others	1.3	1.2	2.7		1.6	0.4	0.0	
Education (years); mean (SD)	16.6 (2.8)	16.7 (2.8)	15.7 (2.8)	†	16.7 (2.7)	16.7 (2.8)	16.0 (3.3)‡	†
Smoking status								
Never	40.3	40.1	42.1	†	38.7	42.4	50.0	†
Former	38.7	38.0	49.5		38.0	44.0	36.0	
Current	21.0	21.9	8.4		23.3	13.6	14.0	
Type 2 diabetes (%)	2.1	2.0	3.6		2.3	0.4	3.6	*
Hypertension (%)	35.5	35.2	38.2		30.1	56.4	45.6	†
Cardiovascular disease§ (%)	5.0	4.5	10.9	†	4.6	5.8	7.2	
Dyslipidaemia (%)	5.2	4.1	20.0	†	6.0	0.8	5.1	†
Age at first visit (years); mean (SD)	57.6 (18.4)	57.6 (18.4)	63.5 (8.4)	†	51.5 (15.7)	81.9 (7.7)	65.7 (13.7)	†
≤20	0.1	0.1	0.0	†	0.1	0.0	0.0	†
21–29	6.0	6.4	0.0		8.0	0.0	0.0	
30–39	15.1	16.3	0.0		19.6	0.0	5.1	
40–49	18.1	19.4	0.0		22.9	0.0	10.1	
50–59	15.3	13.6	38.2		17.9	1.2	17.4	
60–69	14.9	13.0	40.0		16.3	6.2	19.6	
70–79	14.9	14.9	15.4		10.5	25.6	33.3	
80+	15.6	16.3	6.4		4.7	67.2	14.5	
BMI (kg/m^2); mean (SD)	24.9 (3.6)	24.9 (3.5)	25.6 (3.7)	†	24.9 (3.6)	24.7 (3.2)	25.6 (3.3)	†
Underweight (BMI≤18.5); %	1.7	1.8	0.0	*	1.7	2.3	0.0	*
Normal weight (18.5≤BMI≤24.9)	54.2	54.5	50.9		55.2	55.0	44.9	
Overweight (25.0≤BMI≤29.9)	36.5	36.5	39.4		35.1	36.8	46.4	
Obese (BMI≥30)	7.6	7.2	12.7		7.9	5.8	8.7	
Systolic blood pressure (mm Hg); mean (SD)	127.0 (19.0)	126.8 (19.9)	129.3 (19.4)		126.1 (18.7)	134.8 (20.5)‡	135.4 (20.6)‡	†
Diastolic blood pressure (mmHg); mean (SD)	79.1 (10.7)	79.1 (10.8)	79.3 (9.8)		78.9 (10.6)	80.8 (10.2)‡	81.3 (11.3)‡	†
Total cholesterol level (mg/dl); mean (SD)	219.9 (40.6)	217.3 (40.0)	245.5 (38.6)	†	218.9 (40.3)	229.4 (36.1)‡	226.1 (41.8)	†
HDL-C (mg/dl); mean (SD)	49.0 (13.0)	49.8 (12.9)	44.5 (13.0)	†	45.2 (10.5)	45.1 (8.0)	42.6 (7.9)‡	†
Fasting plasma glucose (mg/dl); mean (SD)	98.5 (14.2)	98.0 (13.5)	102.5 (19.3)	†	97.7 (13.3)	97.9 (10.4)	103.7 (15.7)‡	†
Ever-used statins, total¶								
Percentage					8.0	2.3	5.1	†
n					97	6	7	
Ever-used statins, lipophilic								
Percentage					7.3	2.3	3.6	†
n					88	6	5	
Ever-used statins, hydropophilic								
Percentage					1.7	0.0	1.5	
n					21	0	2	

Continued

Table 1 Continued

	Statin ever-use, total¶			Dementia/MCI status			
	All	Statin never-user	Statin ever-user	No dementia or MCI	Incident dementia	Incident MCI	
Mean frequency of statin ever-use (SD)				0.26 (1.1)	0.03 (0.24)‡	0.09 (0.56)	†
Range				0–11	0–2	0–6	

*p<0.10 based on χ^2 test or ANOVA.
†p<0.05 based on χ^2 test or ANOVA.
‡Statistically significant (p<0.05) two-side t test after bonferroni correction, comparing MCI or dementia group to 'No dementia or MCI' group.
§Reported any of the following conditions at first visit: stroke, congestive heart failure, non-fatal myocardial infarction or atrial fibrillation.
¶Statin use prior to onset of dementia or MCI among dementia or MCI cases and after age 50 for all subjects. The mean age of statin use among eligible participants at risk of dementia was 72.7 (SD=9.0; range: 51.2–92.4 years).
HDL-C, high-density lipoprotein cholesterol; Hg, mercury; NH, non-Hispanic.

This same analysis conducted on only AD cases (n=178 failures; N=1561 participants at risk in this model) yielded a HR of 0.30 with a 95% CI 0.10 to 0.95. In addition, when all participants with unknown outcomes were reincluded into the risk set in a sensitivity analysis, both HRs with their 95% CI were not appreciably altered (data not shown).

Similarly, figure 2B shows survival curves for incident MCI and comparing 'statin ever-users' with 'statin never-users' (time-independent variable, definition 1). Both the logrank test and the multivariable-adjusted HR indicated that 'statin ever-users' were at around a threefold lower risk of developing MCI compared with statin never-users (HR=0.32; 95% CI 0.15 to 0.71). Using the time-dependent statin exposure (definition 2) combined with PS approach (figure 3B), the HR was non-significant and attenuated to 0.71 with a 95% CI 0.33 to 1.52. In both analyses, dementia cases were excluded from the risk set. In a sensitivity analysis where dementia cases were reincluded into the risk set, and using time-dependent statin use as main exposure combined with PS approach, the HR remained statistically non-significant (HR=1.07 with a 95% CI 0.49 to 2.30).

Serum cholesterol and risks of dementia and MCI

Table 2 shows results from Cox PH models predicting dementia and MCI risk in relation to statin use ('time-dependent variable') and serum cholesterol exposures. Model 1 (initial visit total cholesterol, dementia risk) indicated that statin use was inversely and significantly related to dementia risk, independently of first-visit TC. In the total population, none of the other serum cholesterol exposures (Models 2–5, dementia risk) considered was associated with dementia risk, independently of statin use. However, when stratifying the analysis by sex (Models 1–5, dementia risk; data not shown), declining TC trajectory over time as predicted at initial visit was found to be significantly associated with dementia risk among men (HR=4.21; 95% CI 1.28 to 13.85), but not among women, independently of statin use. In fact, the interaction term between sex and TC trajectory variable was statistically significant (p=0.012) in a separate model with main effect of sex added.

An elevated initial visit TC (Model 1, MCI risk) was predictive of a lower risk of incident MCI (TC>244.4 vs TC<191.1; HR=0.51 with 95% CI 0.29 to 0.90). Looking at time-dependent TC (Model 3, MCI risk), the third quartile (TC ranging between 211 and 238 mg/dl) was significantly protective against MCI compared with the lowest quartile (TC between 56.3 and 186.2) (HR=0.53; 95% CI 0.30 to 0.94). Moreover, examining the balance between HDL-C and TC (Model 2, MCI risk), initial visit ratios were not significantly associated with the risk of MCI. However, examining this variable in a time-dependent fashion (Model 4, MCI risk) indicated that a ratio of 0.19–0.24 may be optimal in preventing MCI incidence among men and women, combined, compared with a lower ratio of 0.00–0.19, independently of statin use (HR=0.58; 95% CI 0.34 to 0.98), whereas a higher ratio had no significant association with MCI. TC trajectory (Model 5, MCI risk) was not associated with MCI in the total population or within each sex group.

DISCUSSION

Our study investigated the effects of statins and several serum cholesterol exposures on dementia and MCI risks. There are several key findings. However, the most important one was that statin users throughout follow-up had a two- to threefold lower risk of developing dementia (HR=0.41; 95% CI 0.18 to 0.92), but not MCI, when considering time-dependent 'statin use' with propensity score model adjustment. This association remained significant independently of serum cholesterol exposures. Moreover, participants with incident dementia by the end of follow-up had a higher initial TC compared with dementia-free participants. However, this association, as shown later, was strongly confounded by age. Initial TC was higher among statin users than among non-users, and statin use was related directly to initial self-reported dyslipidaemia. In addition, an elevated initial TC was associated with reduced MCI risk (upper quartile (Q_4) vs Q_1: HR=0.51; 95% CI 0.29 to 0.90). Compared with the lowest quartile (Q_1: 0.00–0.19), the HDL-C:TC ratio (time-dependent) in (Q_2: 0.19–0.24) was found to reduce the risk of MCI (HR=0.58; 95% CI 0.34 to 0.98). Finally, among men, the predicted decline in TC trajectory from initial visit was significantly associated with increased dementia risk (HR=4.21; 95% CI 1.28 to 13.85). While these findings were mixed, they show that statin use may be protective against dementia risk independently of serum cholesterol exposures; TC decline may increase the risk of dementia only in men, independently of statin use; whereas other serum cholesterol exposures including time-dependent HDL:TC ratio and initial TC may be at play in modulating risk of MCI, independently of statin use.

Studies related to statin use and dementia risk have produced conflicting results. Some case–control and cross-sectional studies [1 4–7 34] indicated a lower prevalence of statin use among dementia cases. Yet, a number of longitudinal epidemiological studies did not demonstrate a decreased risk of AD, dementia or prevention of cognitive decline and impairment with statin use according to a recent review.[8] This review and meta-analysis of several prospective cohort and case–control studies suggested that the pooled crude ORs in statin users compared with non-users were 0.67 (95% CI 0.54 to 0.82) for dementia risk. However, after adjustment for potential confounders, the pooled OR was 0.77 (95% CI 0.45 to 1.30), suggesting that statins may not be beneficial.[8] At least four other cohort studies were published since this review[9–12]; three showed a protective effect

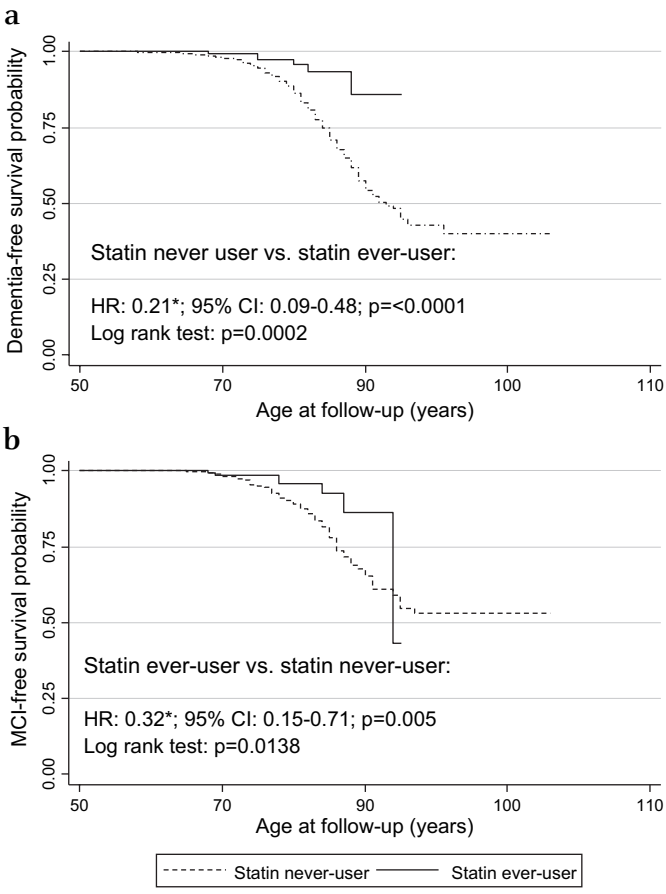

Figure 2 (A) Kaplan–Meier survival curve of time to incidence of dementia by use of statins (time-independent): Cox proportional hazards model and logrank test. A participant is defined as a statin user prior to onset of dementia or mild cognitive impairment (MCI) or by end of follow-up if a non-case but beyond age 50 years. Cox proportional hazards model analysis controlled for sex, education, race/ethnicity, age at first visit (continuous), smoking status at first visit, chronic conditions at first visit (type 2 diabetes, hypertension, dyslipidaemia and cardiovascular disease), body mass index and systolic blood pressure (continuous) at first visit and was based on 1561 participants at risk for dementia and for use of statins (visits at or after 1985) and 252 failures (person-years=37 860). The logrank test was based on 259 incident cases. Six statin-users were observed as incident dementia cases, while 22.7 were expected to become incident cases by chance, which yielded a logrank χ^2 test of 13.93 (1 df); p=0.0002. *p<0.05 for null hypothesis that $\log_e$(HR)=0. (B) Kaplan–Meier survival curve of time to incidence of MCI by use of statins (time-independent): Cox proportional hazards model and logrank test. Statin use was defined in the same way as in figure 2A. Cox proportional hazards model analysis controlled for the same covariates as in figure 2A, but was based on 1308 subjects at risk for MCI and at risk of using statins (visits at or after 1985), with 133 MCI failures (person-years=29 600). The logrank test was based on 138 incident MCI cases. Seven statin-users were observed as incident MCI cases, while 16.2 were expected to become incident cases by chance, which yielded a logrank χ^2 test of 6.07 (1 df); p=0.0138. *p<0.05 for null hypothesis that $\log_e$(HR)=0.

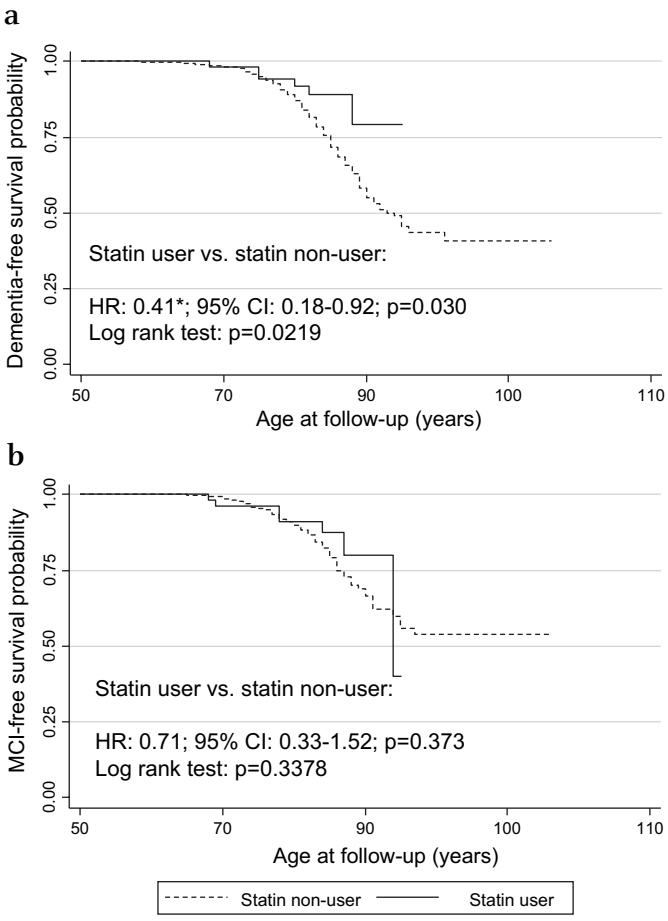

Figure 3 (A) Kaplan–Meier survival curve of time to incidence of dementia by use of statins (time-dependent): Cox proportional hazards model and logrank test. A participant is defined as a statin user at first prescription onwards, prior to onset of dementia or mild cognitive impairment (MCI) or by the end of follow-up if a non-case but beyond age 50 years. Cox proportional hazards model analysis controlled for the same covariates as in figure 2A, but was based on 1560 participants at risk for dementia and for use of statins (visits at or after 1985) and 252 dementia failures (person-years=37842). The logrank test was based on 259 incident cases. Six statin-users were observed incident dementia cases, while 14.3 were expected to become incident cases by chance, which yielded a logrank χ^2 test of 5.26 (1 df); p=0.0219. *p<0.05 for null hypothesis that $\log_e$(HR)=0. (B) Kaplan–Meier survival curve of time to incidence of MCI by the use of statins (time-dependent): Cox proportional hazards model and logrank test. Statin use was defined in the same way as in figure 3A. Cox proportional hazards model analysis controlled for the same covariates as in figure 2A, but was based on 1308 subjects at risk for MCI and for use of statins (visits at or after 1985) and 133 failures (person-years=29 600). The logrank test was based on 138 incident cases. Seven statin-users were observed as incident MCI cases, while 9.9 were expected to become incident cases by chance, which yielded a logrank χ^2 test (1 df) of 0.92; p=0.3378.

against incident dementia (AD in particular),[9 10] and a combination of dementia and MCI.[11] Moreover, a review of nine randomised clinical trials (RCT) with variable samples sizes (22–20 000) and follow-up times (3 weeks to 5 years) indicated that statins do not alter cognitive functioning over time significantly.[35]

Previous studies have also had mixed findings regarding the effect of TC on dementia risk and cognitive functioning. In fact, high TC (>240 mg/dl),[13 15 17] low TC (<200 mg/dl)[14 18] and decrease in TC level over time[16] have been related to deficits in cognitive performance and dementia. For instance, an earlier study conducted on 249 stroke-free community volunteers found that hypercholesterolaemia was a significant independent correlate of memory dysfunction (OR: 3.0; 95% CI 1.4 to 6.6).[13] In contrast, another study carried out among 789 men and 1105 women found that lower naturally occurring TC levels were associated with a poorer performance on cognitive measures, which placed high demands on abstract reasoning, attention/concentration, word fluency and executive functioning.[14]

Table 2 Risk of dementia/mild cognitive impairment (MCI) by statin use prior to dementia (time-dependent) or MCI onset, total cholesterol (tc) (first visit and time-dependent), high-density lipoprotein cholesterol (HDL-C):TC ratio (first visit and time-dependent), and TC trajectory from first visit: results from Cox proportional hazard models; Baltimore Longitudinal Study of Aging

	Dementia				MCI			
	N	n	HR	95% CI	N	n	HR	95% CI
Model 1: first-visit TC	1290	199			1091	106		
Statin user			0.34*	0.14 to 0.84			0.68	0.29 to 1.60
TC (mg/dl)								
Q1: 118.2—191.1			1				1	
Q2: 191.3—215.4			1.45	0.89 to 2.35			0.64	0.35 to 1.15
Q3: 215.6—244.0			1.13	0.69 to 1.87			0.72	0.42 to 1.25
Q4: 244.4—476.0			1.31	0.82 to 2.09			0.51*	0.29 to 0.90
Model 2: first-visit HDL-C:TC ratio	1113	138			975	96		
Statin user			0.40†	0.16 to 1.01			0.55	0.23 to 1.30
HDL-C:TC ratio								
Q1: 0.08—0.17			1				1	
Q2: 0.17—0.21			1.30	0.81 to 2.07			0.94	0.54 to 1.64
Q3: 0.21—0.25			1.14	0.68 to 1.93			1.10	0.61 to 2.00
Q4: 0.24—0.48			1.09	0.58 to 2.06			1.65	0.82 to 3.33
Model 3: time-dependent TC	1458	234			1216	124		
Statin user			0.35*	0.15 to 0.80			0.49†	0.22 to 1.09
TC (mg/dl)								
Q1: 56.3—186.2			1				1	
Q2: 186.5—211.0			1.11	0.77 to 1.59			1.10	0.69 to 1.76
Q3: 211.3—238.7			1.03	0.71 to 1.51			0.53*	0.30 to 0.94
Q4: 239.0—476			0.96	0.65 to 1.40			0.70	0.42 to 1.16
Model 4: time-dependent HDL-C:TC ratio	1244	164			1073	110		
Statin user			0.39*	0.17 to 0.89			0.48†	0.22 to 1.05
HDL-C:TC ratio								
Q1: 0.00—0.19			1				1	
Q2: 0.19—0.24			1.09	0.69 to 1.70			0.58*	0.34 to 0.98
Q3: 0.24—0.29			0.95	0.60 to 1.52			0.65	0.38 to 1.12
Q4: 0.29—0.59			1.00	0.62 to 1.62			0.72	0.41 to 1.26
Model 5: TC change trajectory	1290	199			1091	106		
Statin user			0.33*	0.13 to 0.82			0.67	0.28 to 1.60
TC trajectory from first visit								
Same or upward sloping			1				1	
Downward sloping			1.16	0.78 to 1.73			1.04	0.60 to 1.80
TC (mg/dl) at first visit								
Q1: 118.2—191.1			1				1	
Q2: 191.3—215.4			1.44	0.89 to 2.34			0.64	0.35 to 1.15
Q3: 215.6—244.0			1.14	0.69 to 1.88			0.72	0.42 to 1.26
Q4: 244.4—476.0			1.33	0.83 to 2.13			0.51*	0.29 to 0.90

Cox proportional hazard models with dementia as the outcome controlled for sex, education, race/ethnicity, smoking status, age at first visit, chronic conditions at first visit (type 2 diabetes, hypertension, cardiovascular disease, dyslipidaemia), body mass index and systolic blood pressure at first visit. These potential confounders were selected based on results from table 1, specifically their association with the outcome of interest. Adding diastolic blood pressure to the model did not alter the findings. Plasma glucose level was not included due to a large percentage of missing data at first visit.

*$p<0.05$ based on Wald test for $\log_e(HR)=0$.

†$p<0.10$ based on Wald test for $\log_e(HR)=0$.

n, number of failures observed in the analysis; N, number of subjects in the analysis; Q, quartile.

Our present study found that a drop in TC starting from the first visit increased the risk of dementia among men and that a first-visit TC level above 244 mg/dl may be protective against MCI, independently of statin use. However, when comparing TC at first visit between those who had developed dementia by the end of follow-up and those who did not, TC was higher among dementia participants compared with their non-case counterparts, a highly age-confounded association. Similar to a previous study, the adverse effect of a downward sloping TC over time on incident dementia was particularly found among men.[16]

Both directions of effect, however, carry biological plausibility. For instance, TC at a specific level may be needed for normal neuronal functioning.[36] Alternatively, low cholesterol levels may presage chronic diseases[37] which in turn may be associated with poorer cognitive performance. The relationship may also be a result of a complex interaction between serum TC, TC in cells and certain neurotransmitters such as serotonin.[38] In contrast, the adverse effect of elevated serum TC level, particularly on cognitive decline, can be explained by the existence of subclinical vascular disease.[39] Experimental evidence suggests that cholesterol is in fact capable of shifting amyloid precursor protein

(APP) metabolism from α to β cleavage, which accelerates the production of senile Alzheimer's plaques (Aβ).[40]

Further, our findings regarding the associations between HDL-C:TC ratio versus TC status at first visit and as time-dependent variables versus TC change trajectories on one hand and dementia and MCI risks on the other hand highlight the complexity of the association between serum cholesterol (status vs trajectory) and the balance between 'good' and 'bad' cholesterol on dementia and MCI risks.

The fact that statin's protective effects against dementia and MCI risk are independent of serum cholesterol exposures suggest that statins may be acting through a different pathway in the brain. These multifactorial actions may include preventing atherothrombosis through improvement of endothelial function and inhibition of platelet aggregation or anti-inflammatory activities such as inhibiting C-reactive protein and cytokine responses. Statins have also been shown to have a neuroprotective effect through the enhancement of nitric oxide synthase.[41]

Our study has several strengths. First, it is based on a large prospective cohort study with a long follow-up time (over 20 years), and statin use was measured prior to onset of dementia and MCI. Consequently, and unlike in case–control studies, it is less likely to be confounded by indication[42] (ie, the possibility that dementia cases are less likely to be prescribed statins). In order to address in part that threat to validity, we used a propensity score adjustment method,[33] and our main findings regarding the inverse association between statins and dementia incidence remained significant. Moreover, change trajectories and time-dependent exposure variables were studied, avoiding issues of temporality and reliability due to single measurement. Further, it is one of few longitudinal studies combining analyses of statin use and serum cholesterol in relation to dementia and MCI.[8] Finally, it utilised advanced statistical methods including a combination of multivariable linear mixed models and survival analyses.[43]

Some of our study's limitations include the lack of complete measurements for potentially confounding variables such as plasma fasting glucose. In addition, the BLSA is a sample of convenience; the cohort is not fixed, and recruitment and dropout were continuous throughout the follow-up. Due to the BLSA study's multifaceted nature, some of the data were not of sufficient quality to study detailed exposure effects on cognitive outcomes, including combining dosage of statins, frequency of use and recency of use to obtain standard daily doses as was done by others.[44 45] Finally, many of the analyses involving serum cholesterol exposures (table 2) may require adjustment for multiple testing before one can make an appropriate inference and thus must be examined with caution.

Awaiting large randomised clinical trial (RCT), the beneficial value of statins on dementia and cognitive function can be ascertained only by observational studies. While our study found mixed results regarding serum cholesterol exposures and cognition, it calls for RCTs for statins to enhance that evidence by reducing selection bias and confounding. Moreover, future studies should examine the multifactorial effects of statins and attempt to determine the optimal HDL-C:TC and TC change trajectories for reducing risks of dementia and MCI.

Key findings

Statin users had a two- to threefold lower risk of developing dementia (HR=0.41; 95% CI 0.18 to 0.92), but not MCI, when considering time-dependent 'statin use' with propensity score (PS) model adjustment. This association remained significant independently of serum cholesterol exposures.

What is already known on this subject

Statin use and serum cholesterol reduction have been proposed as preventions for dementia and mild cognitive impairment (MCI).

What this study adds

This study suggests that statins may have multifactorial effects on dementia risk that are independent of cholesterol levels.

Funding This research was supported by the Intramural Research Program of the NIH, National Institute on Aging.

Competing interests None.

Ethics approval Ethics approval was provided by the IRB of the National Institute on Aging for the Baltimore Longitudinal Study of Aging.

Provenance and peer review Not commissioned; externally peer reviewed.

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