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Original Article

Association of statins use and genetic susceptibility with incidence of Alzheimer's disease

Zirong Ye[a,b,e,1], Jiahe Deng[c,1], Xiuxia Wu[d,1], Jingwen Cai[d], Sicheng Li[b], Xiaochun Chen[a,e,*], Jiawei Xin[a,e,*]

[a] Department of Neurology, Fujian Medical University Union Hospital, Fujian Key Laboratory of Molecular Neurology and Institute of Neuroscience, Fujian Medical University, No.29, Xinquan Road, Gulou District, Fuzhou, Fujian Province, 350000, China
[b] Key Laboratory of Health Technology Assessment of Fujian Province, School of Public Health, Xiamen University, Xiang'an Nan Road, Xiang'an District, Xiamen, Fujian Province, 361102, China
[c] School of Clinical Medicine, Fujian Medical University Union Hospital, No.29, Xinquan Road, Gulou District, Fuzhou, Fujian Province, 350000, China
[d] College of Clinical Medicine for Obstetrics & Gynecology and Pediatrics, Fujian Medical University, Fuzhou, Fujian Province, 350000, China
[e] Institute of Clinical Neurology, Fujian Medical University, No.29 Xinquan Road, Gulou District, Fuzhou, Fujian Province, 350000, China

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ABSTRACT

Background: The effect of statins use on the incidence of Alzheimer's disease (AD) is still under debate, and it could be modified by a series of factors.
Objectives: We aimed to examine the association of statins use with the risk of cognitive impairment and AD, and assess the moderating roles of genetic susceptibility and other individual-related factors.
Design: A longitudinal study was conducted from the UK Biobank where individuals completed baseline surveys (2006–2010) and were followed (mean follow-up period: 9 years).
Setting: A population-based study.
Participants: A total of 371,019 dementia-free participants (mean age 56.4 years; 53.6% female).
Measurements: The effects of statins use on cognitive performance and incident AD were examined by using linear regression model and Cox proportional hazards regression model, respectively. We further evaluated the moderating roles of genetic risks and individual-related factors on both multiplicative and additive scales.
Results: The findings showed statins use was associated with an increased risk of AD development [hazard ratio (HR) 1.19 (95% CI: 1.08, 1.30)] compared with no use of statins. We further found significant negative additive interactions of statins use with APOE ε4 allele. Besides, the effects of statins use would be modified by age, sex and cardiovascular diseases (CVDs).
Discussions: A protective effect of statins use was observed in those who carried two APOE ε4 alleles. Also, sex, age and CVDs could modify the effects of statins use, which would provide insights for the guideline of the statins therapy.

1. Introduction

With the acceleration of population ageing, Alzheimer's disease (AD) is becoming one of the greatest public health challenges worldwide [1]. Diseases associated with cognitive impairment lead to increased spendings by governments, communities, families and individuals on protecting the lives of older adults. Cholesterol metabolism has been shown to play an important role in the development of AD [2]. The incidence of AD is correlated with hypercholesterolemia [3]. Therefore, statins, a class of cholesterol-lowering drugs, could reduce blood cholesterol concentration by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR), which may offer a candidate way to prevent cognitive dysfunction and AD [4–6]. One study showed that the statins therapy was associated with slower cognitive decline over a 10-year follow-up [7]. A cohort study suggested that some patients with Alzheimer's which is an indication for lipid-lowering medication may benefit cognitively from statins treatment [8]. And another cohort study in the United States with a median follow-up period of 9.8 years suggested the statins treatment may be associated with a lower risk of AD [6].

* Corresponding authors at: Jiawei Xin, M.D., Xiaochun Chen, M.D., Department of Neurology, Fujian Medical University Union Hospital, Fujian Key Laboratory of Molecular Neurology and Institute of Neuroscience, Fujian Medical University, No.29 Xinquan Road Gulou District, Fuzhou, Fujian Province, 350000, China
E-mail addresses: chenxc998@fjmu.edu.cn (X. Chen), xinjw@fjmu.edu.cn (J. Xin).
[1] These authors contributed equally to this work and share first authorship.

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Notably, statins have also a series of known adverse effects. The most common adverse effects are headaches, altered liver function tests, paraesthesia and gastrointestinal effects (including diarrhea, abdominal pain, and flatulence). Reversible myositis, a rare adverse effect of statins, has also been reported. Furthermore, cognitive impairment due to statins has been shown in case studies, observational researches and randomized controlled trials (RCTs) [9–12]. One cohort study in the UK Biobank also found that statins users have an increased risk of AD [13]. After a review, the U.S. Food and Drug Administration (FDA)'s report on the short-term effects of statins, which included confusion and memory loss as potential adverse effects in the form of cognitive decline, raised the question of whether statins were beneficial to the prevention of cognitive dysfunction and AD [14]. Hence, the effects of statins on both cognitive impairment and the onset of AD remain inconsistent and need to be further replicated.

The effects of statins on cognitive impairment and AD may differ depending on individual-related factors, such as sex, comorbidity, and genetic factors [13,15,16]. For instance, a research based on the Primary Care Electronic Medical Record (EMR) data from the QResearch database (England and Wales) suggested that the risk of AD was reduced with simvastatin or atorvastatin use only in women [17]. Furthermore, the use of statins was associated with a decreased risk of post-stroke cognitive impairment [18], which substantiated that stroke might be a potential moderating factor regarding the relationship between statins use and AD. In addition, a previous research examined that the apolipoprotein E ε4 (APOE ε4) allele could modify the impact of statins on cognitive deterioration. Two additional cohort studies in the US and UK, respectively, substantiated that the protective effect of statins might be associated with the APOE ε4 carrier status [6,13]. Considering other genetic variants beyond APOE ε4 clinically contributing to the pathophysiology of AD and being relevant to cognitive dysfunction [19,20], exploration of the moderating role of other AD-related genes was necessary. Even though previous studies assessed the multiplicative interaction between the use of statins and individual-related factors, no study has examined the additive interactions of greater public health relevance.

Hence, this study aimed to examine the interactions between statins and genetic susceptibility, as well as other individual-related factors (including sex, age and cardiovascular diseases), in relation to AD, which were tested both on the multiplicative and additive scales. Comprehensively identifying genetic risks and individual-related modifiers could improve current practice guidelines regarding statins for the prevention and treatment of AD.

2. Method

2.1. Study population

This study was based on data from the UK Biobank, which is a large population-based prospective cohort study of more than 500,000 participants aged 37–73 years who were recruited between 2006 and 2010 from 22 assessment centers across the England, Scotland, and Wales. All participants provided informed consents through electronic signatures at the baseline assessment. The examination at baseline consisted of a series of cognitive tests, physical measures, and questionnaires involving health status and cognitive function [21]. More detailed information is available on the UK Biobank website (www.ukbiobank.ac.uk).

We used data published in October 2023. Data from participants who were below 40 years of age (n = 7), classified as non-White European (white ethnicity includes British, Irish and any other white background) (n = 30,339), with prevalent neurological or psychiatric disorders (n = 5657), with dementia (n = 89) and with malignant tumor at baseline (n = 38,436), with unclear medication information at baseline (n = 296), with a history of taking both statins and other lipid-lowering medications (n = 5180), with incomplete APOE genotypes data and other single-nucleotide polymorphisms (SNPs), with information for calculating the polygenic risk score associated with AD (n = 28,581) or with missing information on any of the covariates (n = 22,574), were excluded from analyses in our present study. The remaining 371,019 individuals were eligible for analyses in our study. The process of data cleaning is shown in Fig. 1.

2.2. Assessment of statins use

Data regarding a regular use of statins and other cholesterol-lowering medications was collected through an online 'Healthy Work' questionnaire or a verbal interview by a trained nurse at baseline, and reported as medication codes. Medication codes corresponding to statins and non-statin cholesterol-lowering medications were identified respectively (Supplemental Table 1). Statins use was categorized as "yes" for using atorvastatin, fluvastatin, pravastatin, rosuvastatin, simvastatin at baseline and "no" for taking other medications or being unexposed to any drugs ever [22].

2.3. Assessment of incident Alzheimer's disease

Alzheimer's disease was ascertained through linkage to data from primary care, hospital admissions, and death registers during follow-up [23], which was algorithmically defined by health-related outcome preprocessed by the UK Biobank. The duration of the study period from baseline to either event (death or incident AD) or end of study (including loss to follow-up) was calculated in months. Diagnoses were recorded using the International Classification of Diseases-9 (ICD-9) and ICD-10 coding system (Supplemental Table 2).

2.4. Cognitive tests

Participants completed cognitive tests on the touchscreen questionnaire covering four different cognitive domains: visuospatial memory (pairs matching test), reasoning (fluid intelligence test), processing speed (reaction time test), and prospective memory (prospective memory test) [22]. Description of each test is detailed in the Supplemental Table 3. Not all cognitive tests are positively correlated with cognition. For tests of reaction time and pairs matching, higher raw scores indicate worse performance. Thus, the four cognitive scores were recoded so that higher positive values correspond to better cognitive performance. Then, the raw scores from each cognitive test were independently converted to Z-scores for each cognitive domain. This was achieved by subtracting the mean and then dividing by the standard deviation [24]. Finally, Z-scores were summed up to represent the global cognitive Z-score, with higher values reflecting better overall cognitive function.

2.5. APOE ε4 alleles and polygenic risk score (PRS)

The APOE ε4 genotype was determined by two APOE SNPs, rs7412 and rs429358, which were directly inputted by UK Biobank. More detailed information about genotyping process is available elsewhere [25,26]. The number of APOE ε4 alleles was coded as zero (ε2/ε2, ε2/ε3, ε3/ε3), one (ε3/ε4, ε2/ε4) and two (ε4/ε4) (Supplementary Table 4) [27,28].

The PRS for AD was calculated using 38-SNP score (available on the Polygenic Score Catalog online as PGS001775) as the training dataset developed by Ebenauet al [19]. Ebenau et al. selected variants of genome-wide significance from publicly available genome-wide association study summary statistics, which were derived from the International Genomics of Alzheimer's Project [29,30].

Specifically, the hard call threshold 0.1 was controlled by PLINK to eliminate the linkage disequilibrium (LD) with 39 genetic variants and the APOE SNPs (R^2<0.3). One SNP whose minor allele frequency

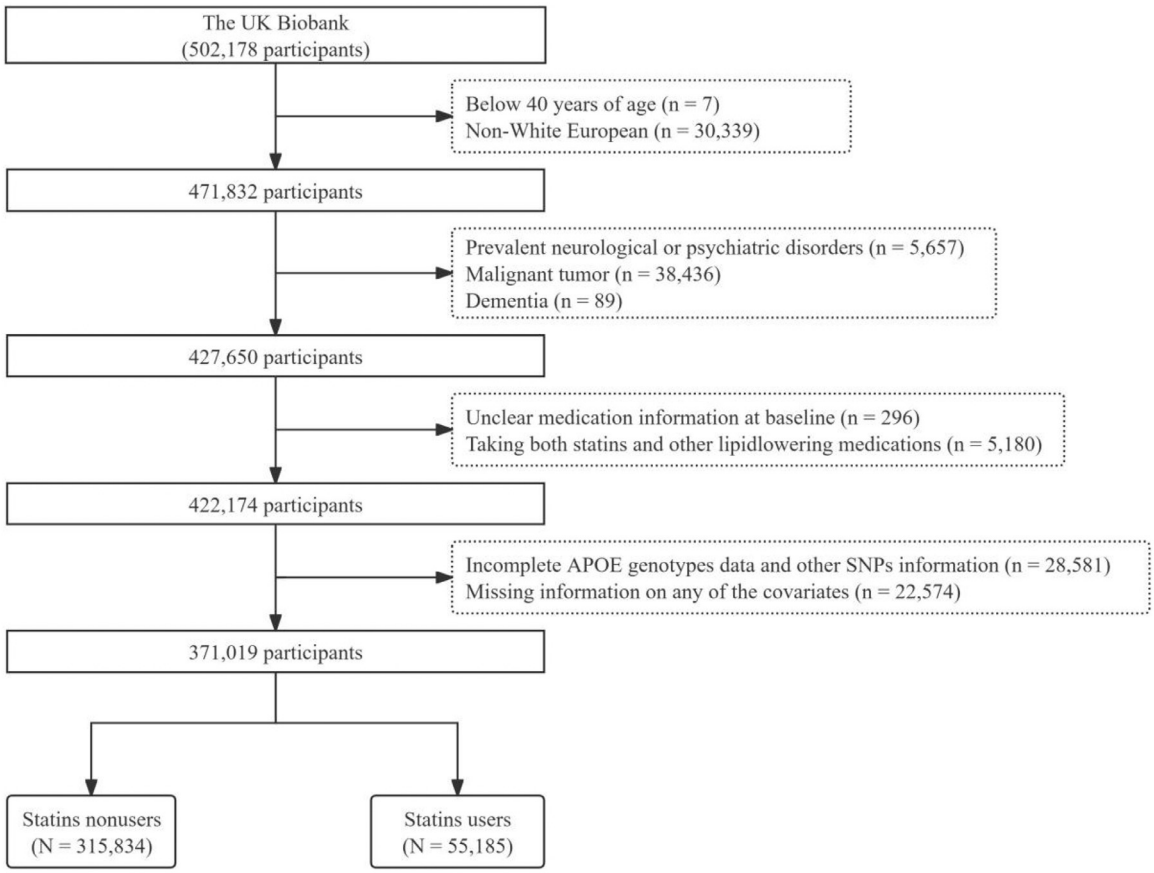

Fig. 1. Workflow of participants' selection at baseline (2006–2010).

<0.005 was excluded. The individual PRS based on the 38 genetic variants was added up the risk alleles weighted by their odds ratios, implemented with the score command in PLINK. No SNPs were ambiguous. The PRS was then divided into quintiles and categorized as "low" (quintiles 1), "intermediate" (quintiles 2–4), and "high" (quintiles 5) groups [31], with a higher score indicating a higher predisposition to AD.

2.6. Covariates

All models were adjusted for variables as follows: age; sex; body mass index (BMI); education level; socioeconomic status; physical activity; smoking status; alcohol consumption; history of diabetes, stroke, coronary heart disease (CHD), heart failure, hypertension, cataract and hearing problems; biological samples: C-reactive protein (CRP) concentrations, blood glucose and low-density lipoprotein (LDL) concentrations; the healthy diet score; self-reported depressive symptoms; social isolation. Covariate adjustment strategy was illustrated in Supplemental Table 5. We also adjusted for the first 10 genetic principal components, genotyping array and relatedness (genetic kinship), when the gene-related factors were involved in the analyses.

2.7. Statistical analysis

Baseline characteristics of the study participants were summarized across the statins use status as percentage for categorical variables, and mean and standard deviation (SD) for continuous variables.

Linear regression model was used to estimate the association between the statins use and cognitive performance. Cox proportional hazards regression was used to examine the association of genetic risk categories and statins use categories with time to incident AD, reporting hazards ratios (HRs) and 95% confidence intervals (CIs). The proportionality of hazards assumption was assessed using the Schoenfeld residuals. Participants were considered at risk of developing the Alzheimer's disease at baseline (2006–2010) and were followed up until the date of first diagnosis, death, loss to follow-up, or the last date of hospital admission (October 30, 2023), whichever came first.

Moreover, an interaction term was added into the model to test the additive and multiplicative interaction between statins use and genetic susceptibility to AD. Genetic susceptibility consists of two parts, APOE ε4-related genetic susceptibility (0,1 or 2 of APOE ε4 alleles) [27,28] and overall genetic susceptibility (low, intermediate, high). The additive interaction was evaluated using two indexes: the relative excess risk due to the interaction (RERI) and the attributable proportion due to the interaction (AP). RERI, or AP of >0, or of <0, indicate synergistic or antagonistic effects, respectively. If the additive interaction was not significant, the CIs of the RERI and AP would include 0. Meanwhile, significant multiplicative interaction occurred when the regression coefficient for the interaction term was significant. Furthermore, the additive and multiplicative interactions between age, sex, and comorbidities (stroke, heart failure, and CHD) and statins on the risk of developing AD were investigated, respectively.

We performed several sensitivity analyses. First, considering the potential bias introduced by the use of other medications, the main model was further adjusted for aspirin use, which may have an effect on the development of AD to a certain extent [32–34]. Second, analyses were restricted to individuals aged between 45 and 50 years old accordingly. Third, we analyzed competing risks by avoiding deaths from non-AD causes as competing events.

All analyses were computed using R software, version 4.3.3. Results were presented as the main effect with a 95% confidence interval. All P

Table 1
The association between statins use with risk of Alzheimer's disease and cognitive performance.

	No. of Events	Model 1* β (95% CI)	Model 2** β (95% CI)	Model 3*** β (95% CI)	Model 4****	Model 5*****
Statins use (Global cognitive Z-score)						
No	99 237	1 [Reference]	1 [Reference]	1 [Reference]	/	/
Yes	18 535	−0.22 (−0.26, −0.19)	−0.10 (−0.13, −0.07)	0.00 (−0.04, 0.04)	/	/
	No. of Events	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
Statins use (Alzheimer's disease)						
No	315 834	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Yes	55 185	1.34 (1.24, 1.46)	1.32 (1.22, 1.43)	1.19 (1.08, 1.30)	1.22 (1.11, 1.33)	1.17 (1.06, 1.29)

* Model 1: Adjusted for age; sex; polygenic risk score (PRS); APOE ε4 allele.
** Model 2: Further adjusted for body mass index (BMI); education level; socioeconomic status; physical activity; smoking status; alcohol consumption; biological samples: CRP concentrations, blood glucose and LDL concentrations; the healthy diet score; self-reported depressive symptoms; social isolation; forced expiratory volume in one second/ forced vital capacity (fev1/ fvc) on the basis of Model 1.
*** Model 3: Further adjusted for history of diabetes, stroke, CHD (angina), heart failure, hypertension, cataract and hearing problems on the basis of Model 2.
**** Model 4: Competing risk model; Adjusted the same concomitant variables as Model 3.
***** Model 5: Further adjusted for asprin use on the basis of Model 3.

values were two-sided, and P<0.05 was considered to denote statistical significance.

3. Results

3.1. Baseline characteristics of participants

This study included 371,019 people with a mean age of 56.4 [standard deviation (SD): 8.05], with a slightly higher proportion of female (53.6%), and 2951 people developed Alzheimer's disease during the follow-up period. We divided the study population according to the statins use status, with 55,185 users and 315,834 nonusers, and Supplemental Table 6 shows the baseline characteristics of participants. Individuals on statins had a higher prevalence of AD (1.65%) than nonusers (0.65%), $p < 0.001$, and a lower global cognitive Z-score [−0.29 (SD: 2.37)] compared with nonusers [0.31 (SD: 2.18)], $p < 0.001$. Despite no significant difference in the APOE ε4 allele status between statins users and nonusers, the distribution in the polygenic risk score was significant difference between two groups, $p = 0.003$. We also found significant differences in age, sex, and history of stroke between statins users and nonusers.

3.2. The effects of statins use on cognitive performance and Alzheimer's disease

Table 1 shows the associations between statins use and the risk of developing AD or impairing cognitive performance. We found that statins use was significantly associated with global cognitive Z-score in the model 1 and model 2, which showed that β was −0.22 (95% CI: −0.26, −0.19) in model 1 and −0.10 (95% CI: −0.13, −0.07) in model 2, respectively. However, after the inclusion of all covariates in model 3, no significant association was seen between the statins use and global cognitive Z-score, and meanwhile, it was significantly associated with the risk of developing AD in these three models. Specifically, in the full-adjusted model (Model 3), statins use was associated with an increased risk of developing AD compared with no statins use, and the HR was 1.19 (95% CI: 1.08, 1.30). In order to further explore the robustness of the results of the model 3, we built a competitive risk model (Model 4), and the HR was 1.22 (95% CI: 1.11, 1.33), which also shows a significant association between statins use and AD. After adjusting for the aspirin, we also observed that statins use was significantly associated with AD (Model 5), and the HR was 1.17 (95% CI: 1.06, 1.29).

Furthermore, we estimated the effects of statins on AD stratified by APOE ε4 allele numbers and the level of PRS (Fig. 2). Although there was no significant association in the two APOE ε4 alleles stratification, statins use was found to increase the risk of AD in the zero APOE ε4 allele group, and the HR was 1.29 (95% CI: 1.11, 1.49) and in the one APOE ε4 allele stratification, the HR was 1.15 (95% CI: 1.01, 1.31). In the intermediate PRS stratification, the HR was 1.22 (95% CI: 1.08, 1.37) and in the high PRS stratification, the HR was 1.26 (95% CI: 1.06, 1.49).

3.3. Joint effects and interactions of statins use and APOE ε4 allele

We explored the interactions between statins use and APOE ε4 alleles. We found significant multiplicative interactions between statins use and two APOE ε4 alleles (P-value for multiplicative interactions = 0.024) on the risk of developing AD. Compared with the control group (participants with zero APOE ε4 allele and without statins use), participants with two APOE ε4 alleles and with statins use had the lowest risk of developing AD, and the HR was 0.72 (95% CI: 0.55, 0.97). The subgroup of participants with zero APOE ε4 allele and with statins use had the most incidence of AD, and the HR was 1.24 (95% CI:1.08, 1.41). We found that the risk of developing AD increased as the number of APOE ε4 allele increased in statins nonusers, while the opposite effect was observed in statins users (Fig. 3). In the sensitivity analysis, considering the potential bias due to aspirin, the multiplicative interactions remained significant ($P = 0.024$). The multiplicative interactions were still significant among individuals aged at least 45 ($P = 0.030$) and at least 50 ($P = 0.033$).

We further found significant negative additive interaction of statins with APOE ε4 allele. Specifically, for statins users with two APOE ε4 alleles (Table 2), the RERI and AP were −0.37 (95% CI: −0.70, −0.03), −0.33 (95% CI: −0.78, −0.06), respectively. This indicated that there would be a 0.37 relative reduced risk because of the additive interaction, accounting for 33% of the risk of developing AD in individuals exposed to both two APOE ε4 alleles and on statins. But significant results were not observed in participants with one APOE ε4 allele and on statins. Besides, we also see the same additive joint interactions in the sensitivity analysis of different age groups. Specifically, the negative additive interactions were fairly constant in individuals at least 50 years old with RERI and AP of −0.35 (95% CI: −0.68, −0.01), −0.32 (95% CI: −0.76, −0.04), and in individuals at least 45 years old with RERI and AP of −0.36 (95% CI: −0.69, −0.01), −0.32 (95% CI: −0.76, −0.05), respectively (Supplemental Table 7). Additionally, similar results were observed in sensitivity analyses that incorporated aspirin as a control variable, the RERI and AP were −0.37 (95% CI: −0.68, −0.06), −0.34 (95% CI: −0.70, −0.09) (Supplemental Table 7).

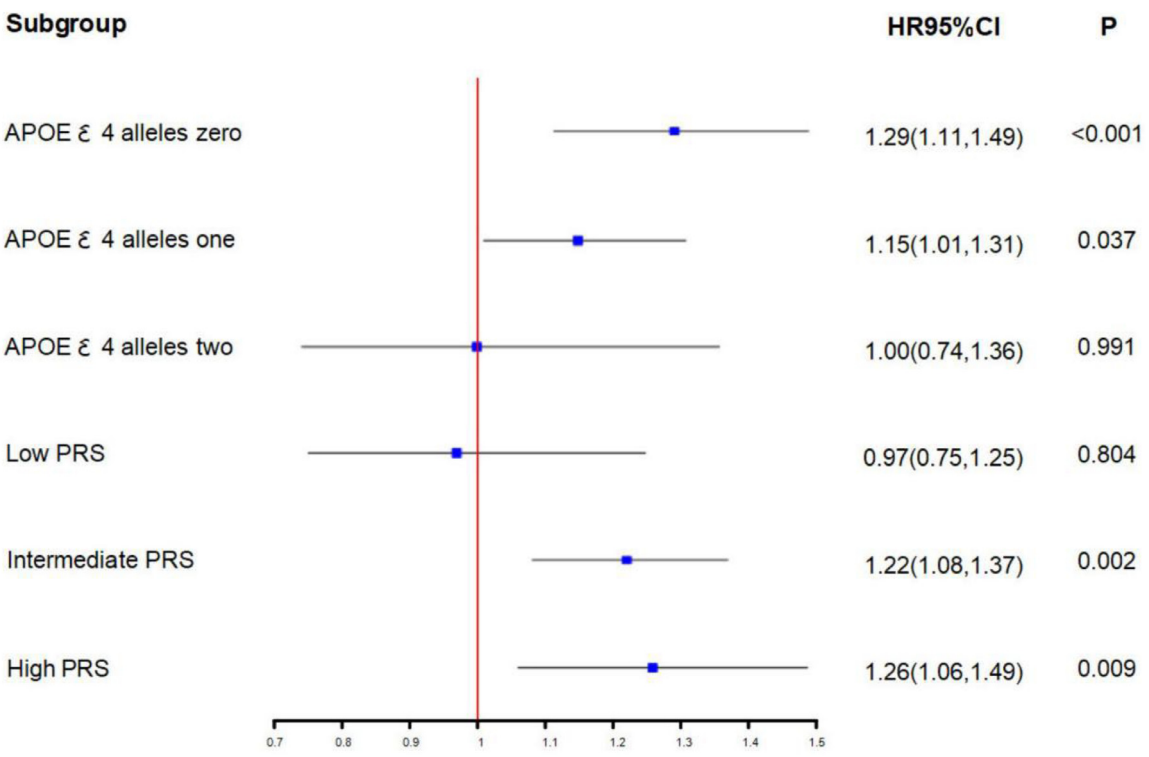

Fig. 2. The effect of statins use on Alzheimer's disease in different subgroups.
Models were adjusted for age; sex; body mass index (BMI); education level; socioeconomic status; physical activity; smoking status; alcohol consumption; history of diabetes, stroke, CHD (angina), heart failure, hypertension, cataract and hearing problems; biological samples: CRP concentrations, blood glucose and LDL concentrations; the healthy diet score; self-reported depressive symptoms; social isolation; forced expiratory volume in one second/ forced vital capacity (fev1/ fvc). Abbreviations: APOE $\varepsilon 4$ = apolipoprotein E $\varepsilon 4$; PRS = polygenic risk score; HR = hazard ratio; CI = confidence interval.

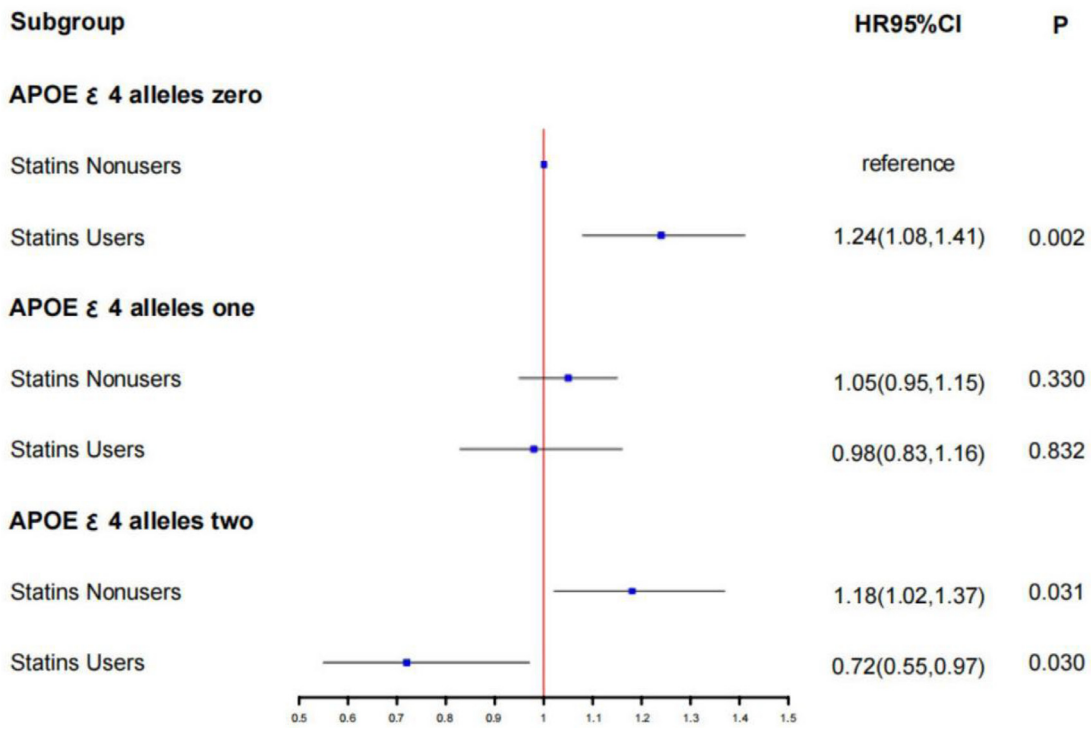

Fig. 3. Joint association between APOE $\varepsilon 4$ allele and statins use in relation to risk of Alzheimer's disease.
Models were adjusted for age; sex; body mass index (BMI); education level; socioeconomic status; physical activity; smoking status; alcohol consumption; history of diabetes, stroke, CHD (angina), heart failure, hypertension, cataract and hearing problems; biological samples: CRP concentrations, blood glucose and LDL concentrations; the healthy diet score; self-reported depressive symptoms; social isolation; forced expiratory volume in one second/ forced vital capacity (fev1/ fvc). Abbreviations: APOE $\varepsilon 4$ = apolipoprotein E $\varepsilon 4$; HR = hazard ratio; CI = confidence interval.

Table 2
Joint effects and interactions of statins use and APOE ε4 allele or PRS.

Subgroup	No. of Events	RERI (95% CI)	AP (95% CI)
Statins * APOE ε4 allele (one)	n = 334 944	−0.01 (−0.2, 0.18)	−0.01 (−0.16, 0.15)
Statins * APOE ε4 allele (two)	n = 190 529	−0.37 (−0.7, −0.03)	−0.33 (−0.78, −0.06)
Statins * PRS (high)	n = 148 409	0.16 (−0.28, 0.59)	0.06 (−0.03, 0.21)
Statins * PRS (intermediate)	n = 296 815	0.15 (−0.15, 0.40)	0.09 (−0.09, 0.25)

Abbreviations: APOE ε4, apolipoprotein E ε4; CI, confidence interval; PRS, polygenic risk score; RERI, relative excess risk due to the interaction; AP, attributable proportion due to the interaction.
Adjusted for age; sex; body mass index (BMI); education level; socioeconomic status; physical activity; smoking status; alcohol consumption; history of diabetes, stroke, CHD (angina), heart failure, hypertension, cataract and hearing problems; biological samples: CRP concentrations, blood glucose and LDL concentrations; the healthy diet score; self-reported depressive symptoms; social isolation, forced expiratory volume in one second/ forced vital capacity (fev1/ fvc).

3.4. Joint effects and interactions of statins use and PRS

We also classified participants according to a combined category of PRS and statins use. Among statins nonusers, we found that the higher the PRS was, the higher the risk of developing AD (Supplemental Figure 1) would be, and a similar trend was observed among statins users. Notably, compared with the control group (participants with low PRS and not on statins), the subgroup of participants with high PRS and on statins had the highest risk of developing AD, and the HR was 2.44 (95% CI: 2.04, 2.91), which was more than double that of the control group. Unfortunately, we didn't observe multiplicative interactions in any groups. In the additive joint analyses, we didn't observe significant additive interactions of PRS with statins use (Table 2), nor did we find them in the sensitivity analyses after stratified by age (Supplemental Table 7).

3.5. Joint effects and interactions of statins use with other individual-related factors

The results for joint effects show that statins use was associated with a reduced risk of AD among people aged 60 years or older, and the HR was 0.54 (95% CI: 0.40, 0.72). Results also show that statins use was associated with an increased risk of developing AD among people under 60 years old, with HR being 2.35 (95% CI: 1.76, 3.12) (Supplemental Figure 2). Statins use was a protective factor against AD in males, with HR being 0.80 (95% CI: 0.68, 0.94) and a risk factor in females, with HR being 1.37 (95% CI: 1.18, 1.51). Statins can reduce the risk of developing AD in people with a history of stroke and heart failure, with the HR being 0.57 (95% CI: 0.36, 0.89) and 0.37 (95% CI: 0.20, 0.68), respectively (Supplemental Figure 2). We also found significant multiplicative interactions between statins use and sex (P-value for multiplicative interactions = 0.025), and stroke (P-value for multiplicative interactions = 0.016), and heart failure (P-value for multiplicative interactions < 0.001) on the risk of developing AD. Also, these interactions were significant on additive scales (in Supplemental Table 8).

4. Discussion

In this study, we found that statins use was significantly associated with an increased risk of incident AD, which was modified by genetic susceptibility and individual-related factors. This study was the first to assess quantitative data about the effects of the additive and multiplicative interactions between statins use and these moderating roles. The effects of statins varied with genetic susceptibility and other individual-related factors, which provided insights for practice guidelines regarding the use of statins.

This study found that statins use was associated with an increased risk of developing AD, but not with short-term cognitive decline after all observed confounders were adjusted. At the beginning of the 21st century, a series of case reports showed that statins may be related to cognitive impairment [9–12]. Recently, two cohort studies also reported adverse effects of statins, which were consistent with our findings. One of them, in the ASPREE cohort, demonstrated that statins use was associated with lower global cognitive performance, especially in episodic memory [32]. The other, from the UK Biobank [13], suggested an adverse effect of statins on AD incidence among the older population, but unfortunately this wasn't discussed in depth. The underling mechanism by which statins are associated with AD is likely linked to blood glucose regulation. Type 2 diabetes (T2D) is considered to aggravate AD [33,34]. Prior reports have found that β-cell function and insulin sensitivity can be affected by statins uses [35], which is associated with decreased brain glucose metabolism [36], thus leading to the potential for neurotoxicity and cognitive impairment [37,38]. Besides, epidemiological studies have shown that statins use was related to increased fasting blood glucose and diabetes progression [39,40]. Therefore, it could be presumed legitimately that statins contribute to AD through blood glucose dysregulation according to above findings. In contrast, the protective effects of statins reported by some studies [6,41] are inconsistent with our results. Of note, the effects of statins could vary with a number of individual-related factors such as genetic diversity, sex, age and even comorbidities, etc. [13,42,43]. Then, evaluating the moderating roles of individual-related factors is extremely relevant for the guideline of statins use.

Intriguingly in our study, the effect of statins on the risk of developing AD was altered by genetic factors, including APOE ε4 and other AD-related SNPs. To be specific, although the adverse effects of statins on AD were observed among noncarriers of the APOE ε4 allele, statins turned out to have lowered the risk of developing AD in APOE ε4 homozygotes, which was similar to the results of previous studies. Donald R. Royall et al. suggested that statins may provide protective effects against ε4 carriers' dementia compared with ε4 non-carriers [44]. And a study in the United States found a significant association of statins with a lower risk of developing AD among participants who carried APOE ε4 allele, but not among those who didn't [6]. As for the PRS calculated by other AD-related SNPs, the adverse effects of statins on AD increased as PRS increased, to our knowledge, which was assessed for the first time. The inconsistent moderating roles of APOE ε4 and other AD-related genes can be explained by the fact that APOE is a kind of apolipoproteins that has a key role in lipid transport both in the plasma and in the central nervous system. In the brain, cholesterol is mainly transported from astrocytes to neurons via low-density lipoprotein receptor (LDLR) family of which APOE is a principle component [45]. Previous studies have indicated that the E4 variant of APOE-dependent cholesterol metabolism dysregulation might be linked to AD-related pathology [46–48]. Consequently, the mechanism of dysregulated APOE expression and statins therapies on hyperlipidemia and hypercholesterolemia might have some overlapping pathways that might translate to reducing the risk of incident AD. Furthermore, this study was the first to validate the association between statins use and APOE ε4 allele on the additive scale, and the significant negative additive interactions were observed, which is more meaningful than the findings of multiplicative interactions. The multiplicative interaction assesses whether the relative risk of statins users vs

non-users varies across APOE ε4 allele carriers groups. By contrast, the additive interaction evaluates whether the difference in statins users' and non-users' absolute risk of developing AD varys with the factors of carrying two and zero APOE ε4 alleles. Therefore, from a public health perspective, the results of additive interaction are more important than the results of multiplicative interactions. Based on these results, it could be speculated that statins use might be an effective method in AD prevention for individuals with two APOE ε4 alleles, while statins should be used with caution for those without APOE ε4 allele.

Notably, we also demonstrated the moderating role of age in the effect of statins on the risk of developing AD. Recent study revealed that reduction for CVDs after a statins therapy were seen in patients aged 75 years or older without increasing risks for severe adverse effects [49]. It is suggested that older adults may benefit more from statins initiation than the young. A research based on the UK Biobank also reported that the effects of statins varied by age, as individuals over 65 showed an improvement in cognition whereas individuals under 65 displayed impaired working memory, which was similar to the findings of our study [50]. In addition, the effect of statins was moderated by sex. Consistent with our findings, Dagliati A et al. revealed that males, in the analyses of cognitive performance in statins users vs. non-users, may obtain more positive effects from statins uses [13]. Interestingly, we also discovered the regulatory effect conferred by cardiovascular diseases regarding statins use and AD. The findings showed a prominent protective effect of statins against AD in participants with stroke or heart failure at baseline. These findings were comparable to a previous study, which concluded that taking statins was correlated with a modest reduction in the risk of dementia after a concussion [51]. A meta-analysis had also shown that post-stroke statins use was associated with decreased risk of cognitive impairment [18]. Overall, these moderating roles of individual-related factors may provide insights for the guideline of statins therapy. Specifically, statins could be used to prevent and treat AD in seniors, males and people with a history of CVDs.

We also acknowledge several potential limitations of this study. First, this sample was restricted to volunteers of European ancestry, and therefore further research is warranted to what degree these findings could be generalized to other ethnic populations. Second, the health outcomes of the studies were collected from hospitalization records and death registers, which may be potential biases toward more severe diseases, and hence some cases of AD were likely to have been missed [21,31,52]. Third, although in the analyses controls were used to adjust for a variety of known potential confounding factors, the possibility of unmeasured bias remained. Fourth, the information of statins was derived from self-reported questionnaires, which may offer a potential source of bias. Fifth, because of the small sample size in each subcategory of statins medication, this study failed to assess the association between different subtypes of statins and incident AD. Finally, because the UK Biobank didn't document the duration of statins use, we were unable to further explore the cumulative effects of the statins.

5. Conclusion

In conclusion, our findings manifested that statins use was significantly associated with an increased risk of incident AD, and it was modified by genetic susceptibility and individual-related factors. Specifically, this risk effect was reversed to a protective effect by factors including the APOE ε4 allele carriers, old age, males and a history of cardiovascular diseases, which provided epidemiological evidence for practice guidelines on AD intervention regarding the use of statins.

Data availability

The data described in this article is available in the UK Biobank (https:// www. ukbiobank.ac.uk/). All researchers can apply to access the UK Biobank database to conduct health-related researches.

Authors' contributions

Zirong Ye, Jiahe Deng and Xiuxia Wu are co-first authors and drafted the manuscript. This study was conceptualized and designed by Jiawei Xin, Zirong Ye, Jiahe Deng, and Xiuxia Wu. Zirong Ye and Jiawei Xin contributed to data acquisition, clean, analysis, and/or interpretation. Critical revision of the manuscript for intellectual content was provided by all authors. All authors read and approved the final manuscript.

Ethical standards

The UK Biobank study was conducted under generic approval from the NHS National Research Ethics Service (approval letter dated 17th June 2011, Ref 11/NW/0382). All participants gave full informed written consent.

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Declaration of competing interest

Authors have no conflict of interest to declare.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjpad.2024.100025.

References

[1] Chowdhary N, Barbui C, Anstey KJ, Kivipelto M, Barbera M, Peters R, et al. Reducing the risk of cognitive decline and dementia: WHO recommendations. Front Neurol 2022;12.
[2] Livingston G, Huntley J, Liu KY, Costafreda SG, Selbæk G, Alladi S, et al. Dementia prevention, intervention, and care: 2024 report of the Lancet standing Commission. Lancet. 2024.
[3] Loera-Valencia R, Goikolea J, Parrado-Fernandez C, Merino-Serrais P, Maioli S. Alterations in cholesterol metabolism as a risk factor for developing Alzheimer's disease: potential novel targets for treatment. J Steroid Biochem Mol Biol 2019;190:104–14.
[4] Zhu XC, Dai WZ, Ma T. Overview the effect of statin therapy on dementia risk, cognitive changes and its pathologic change: a systematic review and meta-analysis. Ann Transl Med 2018;6:435.
[5] Behl T, Kaur I, Fratila O, Brata R, Bungau S. Exploring the Potential of Therapeutic Agents Targeted towards Mitigating the Events Associated with Amyloid-β Cascade in Alzheimer's Disease. Int J Mol Sci 2020;21.
[6] Rajan KB, McAninch EA, Wilson RS, Dhana A, Evans-Lacko S, Evans DA. Statin Initiation and Risk of Incident Alzheimer Disease and Cognitive Decline in Genetically Susceptible Older Adults. Neurology 2024:102.
[7] Geifman N, Brinton RD, Kennedy RE, Schneider LS, Butte AJ. Evidence for benefit of statins to modify cognitive decline and risk in Alzheimer's disease. Alzheimers Res Ther 2017;9.
[8] Petek B, Häbel H, Xu H, Villa-Lopez M, Kalar I, Hoang MT, et al. Statins and cognitive decline in patients with Alzheimer's and mixed dementia: a longitudinal registry-based cohort study. Alzheimers Res Ther 2023:15.
[9] Bettermann K, Arnold AM, Williamson J, Rapp S, Sink K, Toole JF, et al. Statins, risk of dementia, and cognitive function: secondary analysis of the ginkgo evaluation of memory study. J Stroke Cerebrovasc Dis 2012;21:436–44.

[10] Evans MA, Golomb BA. Statin-associated adverse cognitive effects: survey results from 171 patients. Pharmacotherapy 2009;29:800–11.
[11] Orsi A, Sherman O, Woldeselassie Z. Simvastatin-associated memory loss. Pharmacotherapy 2001;21:767–9.
[12] Wagstaff LR, Mitton MW, Arvik BM, Doraiswamy PM. Statin-associated memory loss: analysis of 60 case reports and review of the literature. Pharmacotherapy 2003;23:871–80.
[13] Dagliati A, Peek N, Brinton RD, Geifman N. Sex and APOE genotype differences related to statin use in the aging population. Alzheimers Dement 2021;7:e12156.
[14] Britannica TEoEhwbctF-a-D-AFood and Drug Administration. Encyclopedia Britannica 2024.
[15] Geifman N, Brinton RD, Kennedy RE, Schneider LS, Butte AJ. Evidence for benefit of statins to modify cognitive decline and risk in Alzheimer's disease. Alzheimers Res Ther 2017;9:10.
[16] Reuben DB, Kremen S, Maust DT. Dementia prevention and treatment: a narrative review. JAMA Intern Med 2024;184:563–72.
[17] Power MC, Weuve J, Sharrett AR, Blacker D, Gottesman RF. Statins, cognition, and dementia—systematic review and methodological commentary. Nat Rev Neurol 2015;11:220–9.
[18] Yang Z, Wang H, Edwards D, Ding C, Yan L, Brayne C, Mant J. Association of blood lipids, atherosclerosis and statin use with dementia and cognitive impairment after stroke: a systematic review and meta-analysis. Ageing Res Rev 2020;57:100962.
[19] Ebenau JL, Van Der Lee SJ, Hulsman M, Tesi N, Jansen IE, Verberk IMW, et al. Risk of dementia in *APOEε*4 carriers is mitigated by a polygenic risk score. Alzheimer's Dement: Diagnosis, Assessment Dis Monit 2021;13.
[20] Loy CT, Schofield PR, Turner AM, Kwok JB. Genetics of dementia. Lancet 2014;383:828–40.
[21] Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, et al. UK Biobank: an Open Access Resource for Identifying the Causes of a Wide Range of Complex Diseases of Middle and Old Age. PLoS Med. 2015;12:e1001779.
[22] Gentreau M, Rukh G, Miguet M, Clemensson LE, Alsehli AM, Titova OE, et al. The Effects of Statins on Cognitive Performance Are Mediated by Low-Density Lipoprotein, C-Reactive Protein, and Blood Glucose Concentrations. J Gerontol: Ser A 2023;78:1964–72.
[23] The UK Biobank Showcase User Guide, https://biobank,ctsy,ox,ac,yk/wbbdatan/showcaseUserGuide.pdf. Accessed 26 February 2024.
[24] Cong L, Ren Y, Wang Y, Hou T, Dong Y, Han X, et al. Mild cognitive impairment among rural-dwelling older adults in China: a community-based study. Alzheimers Dement 2023;19:56–66.
[25] Bycroft C, Freeman C, Petkova D, Band G, Elliott LT, Sharp K, et al. The UK Biobank resource with deep phenotyping and genomic data. Nature 2018;562:203–9.
[26] Palpatzis E, Bass N, Jones R, Mukadam N. Longitudinal association of apolipoprotein E and sleep with incident dementia. Alzheimer's Dement 2022;18:888–98.
[27] Ma H, Li X, Zhou T, Wang M, Heianza Y, Qi L. Long-term exposure to low-level air pollution, genetic susceptibility and risk of dementia. Int J Epidemiol 2023;52:738–48.
[28] Lyall DM, Ward J, Ritchie SJ, Davies G, Cullen B, Celis C, et al. Alzheimer disease genetic risk factor*APOE*ε4 and cognitive abilities in 111,739 UK Biobank participants. Age Ageing 2016;45:511–17.
[29] de Rojas I, Moreno-Grau S, Tesi N, Grenier-Boley B, Andrade V, Jansen IE, et al. Common variants in Alzheimer's disease and risk stratification by polygenic risk scores. Nat Commun 2021;12:3417.
[30] Sims R, van der Lee SJ, Naj AC, Bellenguez C, Badarinarayan N, Jakobsdottir J, et al. Rare coding variants in PLCG2, ABI3, and TREM2 implicate microglial-mediated innate immunity in Alzheimer's disease. Nat Genet 2017;49:1373–84.
[31] Lourida I, Hannon E, Littlejohns TJ, Langa KM, Hyppönen E, Kuzma E, Llewellyn DJ. Association of Lifestyle and Genetic Risk With Incidence of Dementia. JAMA 2019;322:430–7.
[32] Lu G, Li Z. Statin Therapy on Cognitive Decline and Incident Dementia. J Am Coll Cardiol 2021;78:e101.
[33] Barbiellini Amidei C, Fayosse A, Dumurgier J, Machado-Fragua MD, Tabak AG, van Sloten T, et al. Association Between Age at Diabetes Onset and Subsequent Risk of Dementia. JAMA 2021;325:1640–9.
[34] Janson J, Laedtke T, Parisi JE, O'Brien P, Petersen RC, Butler PC. Increased risk of type 2 diabetes in Alzheimer disease. Diabetes 2004;53:474–81.
[35] Betteridge DJ, Carmena R. The diabetogenic action of statins - mechanisms and clinical implications. Nat Rev Endocrinol 2016;12:99–110.
[36] Hirvonen J, Virtanen KA, Nummenmaa L, Hannukainen JC, Honka MJ, Bucci M, et al. Effects of insulin on brain glucose metabolism in impaired glucose tolerance. Diabetes 2011;60:443–7.
[37] Sodero AO, Barrantes FJ. Pleiotropic effects of statins on brain cells. Biochimica et Biophysica Acta (BBA) - Biomembranes 2020;1862:183340.
[38] German CA, Liao JK. Understanding the molecular mechanisms of statin pleiotropic effects. Arch Toxicol 2023;97:1529–45.
[39] Kim J, Lee HS, Lee KY. Effect of statins on fasting glucose in non-diabetic individuals: nationwide population-based health examination in Korea. Cardiovasc Diabetol 2018;17:155.
[40] Mansi IA, Chansard M, Lingvay I, Zhang S, Halm EA, Alvarez CA. Association of Statin Therapy Initiation With Diabetes Progression: a Retrospective Matched-Cohort Study. JAMA Intern Med 2021;181:1562–74.
[41] Torrandell-Haro G, Branigan GL, Vitali F, Geifman N, Zissimopoulos JM, Brinton RD. Statin therapy and risk of Alzheimer's and age-related neurodegenerative diseases. Alzheimer's Dement: Transl Res Clin Interven 2020;6.
[42] Jamshidnejad-Tosaramandani T, Kashanian S, Al-Sabri MH, Kročianová D, Clemensson LE, Gentreau M, Schiöth HB. Statins and cognition: modifying factors and possible underlying mechanisms. Front Aging Neurosci 2022;14.
[43] Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. Lancet. 2020;396:413–46.
[44] Royall DR, Palmer RF. Statin use moderates APOE's and CRP's associations with dementia and is associated with lesser dementia severity in ε4 carriers. Alzheimer's Dement 2023.
[45] Liu C-C, Kanekiyo T, Xu H, Bu G. Apolipoprotein E and Alzheimer disease: risk, mechanisms and therapy. Nat Rev Neurol 2013;9:106–18.
[46] Hatters DM, Peters-Libeu CA, Weisgraber KH. Apolipoprotein E structure: insights into function. Trends Biochem Sci 2006;31:445–54.
[47] Kingwell K. Oligodendrocytes take centre stage in APOE4-linked Alzheimer disease. Nat Rev Drug Discov 2023;22:15.
[48] Montagne A, Nation DA, Sagare AP, Barisano G, Sweeney MD, Chakhoyan A, et al. APOE4 leads to blood-brain barrier dysfunction predicting cognitive decline. Nature 2020;581:71–6.
[49] Xu W, Lee AL, Lam CLK, Danaei G, Wan EYF. Benefits and Risks Associated With Statin Therapy for Primary Prevention in Old and Very Old Adults: real-World Evidence From a Target Trial Emulation Study. Ann Intern Med 2024;177:701–10.
[50] Alsehli AM, Olivo G, Clemensson LE, Williams MJ, Schiöth HB. The Cognitive Effects of Statins are Modified by Age. Sci Rep 2020;10.
[51] Redelmeier DA, Manzoor F, Thiruchelvam D. Association Between Statin Use and Risk of Dementia After a Concussion. JAMA Neurol 2019;76:887–96.
[52] Nedelec T, Couvy-Duchesne B, Darves-Bornoz A, Couronne R, Monnet F, Gantzer L, et al. A comparison between early presentation of dementia with Lewy bodies, Alzheimer's disease, and Parkinson's disease: evidence from Routine Primary Care and UK Biobank Data. Ann Neurol 2023;94:259–70.