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Association Between Statin Use and Depressive Symptoms in a Large Community–Dwelling Older Population Living in Australia and the USA: A Cross–Sectional Study

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Conflict of interest Bruno Agustini, Mohammadreza Mohebbi, Robyn L. Woods, John J. McNeil, Mark R. Nelson, Raj C. Shah, Anne M. Murray, Michael E. Ernst, Christopher M. Reid, Andrew Tonkin, Jessica E. Lockery and Michael Berk have not conflicts of interest that are directly relevant to the content of this article.

Ethics approval The ASPREE study was conducted in accordance with the Declaration of Helsinki 1964 as revised in 2008, the NHMRC Guidelines on Human Experimentation, the federal patient privacy (HIPAA) law and the International Conference of Harmonisation Guidelines for Good Clinical Practice. ASPREE also follows the Code of Federal Regulations as it relates to areas of clinical research.

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Abstract

Background—Statin use has been frequently associated with depressive symptoms in an older population. However, the nature of this association is uncertain in the literature. In this study, we aimed to investigate the association of statin intake and the prevalence of depressive symptoms in healthy community-dwelling older adults living in Australia and the USA.

Methods—We analysed baseline data from 19,114 participants, over 70 years of age (over 65 years of age, if from an ethnic minority). The association of self-reported statin use and prevalence of depressive symptoms, as measured by a validated depression scale [Center for Epidemiological Studies Depression Scale (CES-D 10)], was determined using logistic regression models. Multivariable logistic models were implemented to account for important demographics and other lifestyle and socioeconomic factors, such as sex, age, living status, education and smoking history.

Results—A total of 5987 individuals were statin users. Of those, 633 (10.6%) had depressive symptoms (CES-D 10 cut-off ≥ 8), compared with 1246 (9.5%) of the non-statin users. In the unadjusted model, statin use was associated with an increase in prevalence of depressive symptoms (odds ratio 1.13, confidence interval 1.02–1.25, $p = 0.02$). However, after adjusting for important demographic and socioeconomic factors, the use of statins was not significantly associated with depressive symptoms (odds ratio 1.09, confidence interval 0.98–1.20, $p = 0.11$). In secondary analyses, only simvastatin was marginally associated with an increased prevalence of depressive symptoms. Statins were associated with a decreased prevalence of depressive symptoms in individuals with severe obesity (body mass index > 35 kg/m^2) and an increased prevalence in participants between 75 and 84 years of age.

Conclusion—This study in a large community-dwelling older population did not show any association of statins with late-life depressive symptoms, after accounting for important socioeconomic and demographic factors. Confounding by indication is an important issue to be addressed in future pharmacoepidemiologic studies of statins.

1 Introduction

The presence of chronic health problems tends to increase with age and medical conditions frequently cluster in older individuals [1]. Increased numbers of medical comorbidities are associated with increased consumption of medications, with multiple drugs targeting multiple disorders. As the world's population gets older, identifying which drugs are potentially associated with depression, whether protecting or increasing the risk, becomes critical to guide medical decision making and adequately tackle depression in later life [2].

Statins are a group of cholesterol-lowering drugs with anti-inflammatory and antioxidant properties [3]. Because depression (at least subgroups of it) has been consistently associated with inflammatory and oxidative disturbances [4], it was hypothesised that statins might have a beneficial effect in depression prevention [5]. Consequently, the relationship between statin use and depression has been under investigation for many years, with conflicting findings. While some studies found that statin use protects against depressive symptoms [6–8], others found that these medications might in fact increase this risk [9–12], while others found no relationship at all [13]. Heterogeneity in study designs, different instruments for measuring depression, lack of control for confounding factors and mainly distinct study

populations may explain a significant part of these discrepancies. Moreover, most of the studies published so far concern younger populations and very few addressed the role of statins in depression in later life.

Statins are one of the most prescribed drug classes worldwide, with confirmed benefits in reducing cardiovascular morbidity and mortality in patients with established cardiovascular disease (CVD) [14, 15]. However, there is an ongoing debate about their role in the primary prevention of a range of conditions in a healthy aged population [16–18]. While these drugs are more widely indicated, especially after negative results of some aspirin trials [19–21], it is important to understand their potential impact on mental health and quality of life in this vulnerable age group. Therefore, using cross-sectional data of a very large population of healthy older adults without known atherosclerotic CVD, living in the community, we aimed to investigate the association of statin use and the prevalence of depressive symptoms in this healthy aged population.

2 Methods

2.1 Participants

This cross-sectional study is a sub-study of a large, population-based, randomised controlled trial on the effects of aspirin for primary prevention in an older population, the ASPirin in Reducing Events in the Elderly (ASPREE) study [22], which recruited a total of 19,114 participants, over 70 years of age (> 65 years of age if from an ethnic minority) from Australia and the USA. Patients were recruited from general practice, with general practitioners as ASPREE co-investigators. After a phone screen, participants were invited to a baseline interview at the general practitioner's clinic for eligibility and baseline assessments. Recruitment ended in December 2014.

2.2 Inclusion Criteria

Inclusion criteria were community-dwelling men and women 70 years of age and older (US minority 65 years of age and older) who were willing and able to provide informed consent.

2.3 Exclusion Criteria

Exclusion criteria in the ASPREE study were a past history of cardiovascular events or established CVD or atrial fibrillation; dementia or a score of < 78 on the Modified Mini-Mental State examination; disability as defined by severe difficulty or inability to perform any one of the Katz activities of daily living; a condition with a high current or recurrent risk of bleeding (e.g. cerebral aneurysm or cerebral arteriovenous malformation, any bleeding diathesis, gastrointestinal malignancy, recent peptic ulcer, liver disease, oesophageal varicosities, uraemia, aortic aneurysm or any other condition known to be associated with a high risk of serious bleeding); anaemia; a condition likely to cause death within 5 years (such as terminal cancer or obstructive airways disease); current use of other antiplatelet or antithrombotic medication, current use of aspirin for secondary prevention and uncontrolled hypertension.

2.4 Instruments

Once enrolled in the study, subjects underwent a comprehensive assessment with multiple physical and mental health measures [22]. At baseline, they answered to a sociodemographic questionnaire that included age, education, sex, smoking status, alcohol use, living status and self-reported presence and/or history of medical conditions, including depression, hyperlipidaemia, hypertension and diabetes mellitus. They also had their height, weight [used to calculate body mass index (BMI)] and abdominal circumference measured, along with blood pressure and heart rate. Blood samples were collected for laboratory measures, including lipid profile, glucose, creatinine and haemoglobin levels. The presence of hypertension was defined as a combination of direct blood pressure measures (systolic blood pressure > 140 mmHg or diastolic blood pressure > 90 mmHg) or taking an antihypertensive medication. The presence of diabetes was defined as an elevated fasting blood glucose (≥ 7 mmol/L) or treatment for diabetes or self-report.

2.5 Medication Use

The number and type of concomitant self-reported medication use were also included in the baseline questionnaire and participants were asked to bring in their prescribed medications or a list of these. Trade and/or generic names were collected and coded according to the Anatomical Therapeutic Chemical Classification System of the World Health Organization. This was the information utilised in this study as indicative of prevalent statin use and the number of concomitant medications, including antidepressants and non-steroidal anti-inflammatory agents.

2.6 Depression Measurement

The Centre for Epidemiological Studies Depression Scale (CES-D 10) was used to quantify the presence of depressive symptoms [23]. The CES-D 10 is a self-completed questionnaire that scores the severity of depressive symptoms in general populations. Participants responded to each item of the scale by rating the frequency of each mood symptom “during the past week” on a four-point scale. All items are then summed up and provide a score that ranges from 0 to 30 [24]. This instrument has previously shown comparable accuracy to the full version of the CES-D ($\kappa = 0.97$) in classifying participants with depressive symptoms [23]. Specifically, in the context of depression in the elderly, construct validity of the CES-D 10 showed that a single score was a reliable and valid measure of depression in this population [25]. When compared to a formal psychiatric diagnosis of late-life depression, the scale was shown to have a sensitivity of 97% and a specificity of 84% in this population [26]. In this study, a cut-off of ≥ 8 was used to define an increased prevalence of depressive symptoms. This cut-off was shown to have high sensitivity (1.00) and moderate specificity (0.47), with an average misclassification rate of 23.5%, in an older Chinese population [27].

2.7 Data Quality and Governance

The study benefits from high-quality data as this is a sub-study of a randomised control trial. The ASPREE Steering Committee is responsible for data management and access [22]. All data were collected according to the same measurement protocol, with very small percentages of missing data.

2.8 Statistical Analysis

Baseline sample characteristics of statin users and non-users were compared using independent sample *t* tests for continuous measures or Chi-square tests for categorical measures. The association of statin use with dichotomised depressive symptoms was determined using logistic regression models and odds ratios (ORs) and 95% confidence intervals (CIs) were reported. Multivariable logistic models were implemented to account for important demographics and other lifestyle and socioeconomic factors, namely sex, education, smoking and living status. To avoid multicollinearity, subgroup analysis was performed to account for metabolic and other risk factors individually. Stratified analyses were performed for age (≤ 74, 75–84, 85 + years), BMI (≤ 25, 25–30, 30–35, 35 + kg/m^2), presence of diabetes and high blood pressure, and abdominal circumference (≥ 88 cm in female individuals, ≥ 102 cm in male individuals) [28]. Subgroup analysis according to antidepressant and anti-inflammatory use was also included. All statistical tests were two tailed and a *p* value of < 0.05 was considered to indicate statistical significance. All analyses were performed using STATA software, Version 15.0 (StataCorp. 2017. College Station, TX: StataCorp LLC).

3 Results

Table 1 shows the characteristics of participants according to statin use status. Of 19,114 participants, 16,703 (87.4%) were from Australia and 2411 (12.6%) from the USA. Mean age was 75 years, and the oldest participant was 98 years. Of those, 10,783 (56.4%) were female. In total, 12,779 (66.9%) participants lived in a private home with family, friends or spouse, 18,263 (95.6%) had an English-speaking background, and 4276 (22.4%) were born overseas. Of 1664 ethnic minority participants, 1323 (80%) were from the USA. Current smoking was reported by 735 (3.9%) and 14,642 (76.6%) were current alcohol consumers.

Overall, 1879 subjects (9.8%) had a CES-D 10 score of ≥ 8. Only four individuals did not have the complete CES-D 10 scores (0.02%). Depressive symptoms were more prevalent in female individuals (*n* = 1248; 11.6%) compared with male individuals (*n* = 631; 7.6%). Increased depressive symptoms were also more prevalent in individuals educated for 12 years or less, living alone or in a residential care facility, and in ethnic minorities and current smokers. Antidepressants were used by 2145 individuals (11.2%). Of those, 456 (21.3%) remained depressed according to our cut-off, while 1688 (78.7%) were found to be in remission or were taking antidepressants for another reason other than depression. Anti-inflammatory drugs were used by 2702 individuals (14.4%). Of those, 315 (11.7%) presented with depressive symptoms.

Statin use was self-reported in 5987 individuals (31% of total participants). Atorvastatin was the most frequently used statin (*n* = 2268), followed by simvastatin (*n* = 1777), rosuvastatin (*n* = 1527) and pravastatin (*n* = 348). Lovastatin, fluvastatin and pitavastatin had a combined number of users of 72. After logistic regression of each specific statin compound, only simvastatin was marginally associated with increased depressive symptoms (Table 2). All other prevalent statin compounds were not significant at the 0.05 level: atorvastatin (OR 0.99, 95% CI 0.86–1.15, *p* = 0.95), lovastatin (OR 1.12, 95% CI 0.48–2.62, *p* = 0.78), pravastatin (OR 1.06, 95% CI 0.75–1.5, *p* = 0.75) and rosuvastatin (OR 1.11, 95% CI 0.94–

1.32, $p = 0.21$). Fluvastatin and pitavastatin were excluded from this analysis because of a low number of users.

Blood lipid profile was significantly different among groups, with statin users presenting with lower levels of total cholesterol, low-density lipoprotein, and high-density lipoprotein, and higher levels of triglycerides. Statin users more often had the presence of diabetes, high blood pressure and elevated abdominal circumference. They also tended to use more concomitant medications compared with non-statin users (Table 1).

The crude and adjusted analyses for examining the association between statin and simvastatin use and depressive symptoms (defined by a CES-D 10 score of ≥ 8) are summarised in Table 2. In the crude analysis, both statin and simvastatin use were significantly associated with increased depressive symptoms. However, after adjusting for important demographic and socioeconomic factors, namely sex, age, living status, education and smoking history, statins were no longer significantly associated with an increased prevalence of depressive symptoms (OR 1.09, 95% CI 0.98–1.20, $p = 0.11$). After adjustment of each individual statin, only simvastatin remained closely significantly associated with increased odds (+ 16%) of depressive symptoms in this population ($p = 0.05$).

Subgroup analyses are shown in Table 3. Association between statin use and depressive symptoms was significant in the 75–84 years of age subgroup. There was a 21% increase in the prevalence of depressive symptoms among statin users in this group after accounting for important demographics and socioeconomic factors. There was also an association of depressive symptoms in individuals with a BMI of 25–30 kg/m^2, and over 35 kg/m^2 subgroup analyses. There was a marginally significant 16% increase in the prevalence of depressive symptoms in statin users with a BMI of 25–30 kg/m^2. Conversely, individuals taking statins with a BMI over 35 kg/m^2 showed a 31% decrease in the prevalence of depressive symptoms compared with nonstatin users. There were no significant differences between groups according to antidepressant or anti-inflammatory drug use. No other subgroups were statistically significantly associated with depressive symptoms.

4 Discussion

The primary outcome of this comprehensive study in a very large and healthy community-dwelling older population failed to show an association of statin use with an increased prevalence of depressive symptoms, after adjusting for major confounders. In additional exploratory analyses, associations of individual statin compounds were conducted because their relative lipophilicity affects their ability to cross the blood–brain barrier. In that post-hoc analysis, simvastatin use, after adjustment, was marginally associated with an increased prevalence of depressive symptoms.

One possible explanation for our findings could be participants' characteristics. Table 1 shows that statin users tend to include more female individuals and are generally less educated than the non-statin users, factors associated with higher rates of depression [29]. They also differ in important physical characteristics. They have higher BMIs and

abdominal circumference (direct measures of obesity) as well as higher rates of diabetes and hypertension (Table 1). Each of these conditions has been previously linked to an increased risk of late-life depression [30–32]. Often, these factors tend to coalesce in the metabolic syndrome. Criteria for metabolic syndrome include elevated blood pressure, abdominal obesity, dyslipidaemia and increased blood sugar [33]. The presence of metabolic syndrome has been associated with symptom severity and chronicity in late-life depression, as well as poorer antidepressant response [34]. After these factors were taken into consideration in our study, and after subgroup analyses, the increased prevalence of depression in statin users was no longer statistically significant. Such confounding by indication is an important factor in other conditions and medications linked with possible neuropsychiatric adverse events [35, 36]. To address this issue, we performed multivariate analyses for all significant confounding factors associated with depression in our sample, one of the main strengths of this study.

An alternative method of tackling confounding by indication is the use of propensity-matched scores, mainly in cohort studies [37]. Our results agree with two large propensity-matched scores studies of statin use and depression. After pairing statin users and non-users according to important characteristics such as sex, age and several other potential confounders, they both failed to find an association of statin use and depression [38, 39]. Those authors suggest other factors drive this association, including residual confounding and downstream effects of the statin prescription, such as visiting a doctor more often. However, both studies were not conducted in a specific older population. Randomised controlled trials are the most definitive means of eliminating confounding by indication, and here, most trials of statins as adjuvants for depression are positive, showing reductions in depressive symptoms [7].

A possible explanation for a lack of protective effect of statins against depression in our study is the fact that late-life depression differs substantially from depression in other age groups regarding its aetiology and prognosis [40]. Late-life depression has been shown to be more associated with vascular damage and morphologic alterations of brain structures [41, 42]. It may be that in younger age groups, before brain change has occurred, a greater benefit from anti-inflammatory strategies may arise. Once brain change has happened, anti-inflammatory drugs may be unable to reverse the process, although they might still play a role in preventing it at early stages.

The only longitudinal study conducted in an aged population was performed as part of the Singaporean Longitudinal Ageing Studies cohort in 2009. In this study of 1803 individuals living in the community, the authors found no association between statin use and depressive symptoms (as measured by the Geriatric Depression Scale) after 1.5 years of follow-up, in their adjusted analysis ($\beta = -0.12$, $p = 0.23$). Post-hoc findings suggested a protective effect of statins in women ($\beta = -0.29$, $p = 0.02$) and an association with more depressive symptoms in men, particularly those with medical comorbidities ($\beta = 0.63$, $p = 0.04$) and multiple drug use ($\beta = 0.74$, $p = 0.02$) [43]. This sex difference conflicts with the findings of Williams et al. that found a protective effect of statin use against depression in men [6].

On subgroup analysis, there was an increased prevalence of depressive symptoms in statin users between 75 and 84 years of age. This might reflect the same confounding by indication and the prolonged survival of patients with chronic conditions in this age group. In addition, inflation of type I error due to performing a number of subgroup analyses may also play a role. We found that participants with BMI over 35 kg/m^2 were the only group in which statins appear to be a protective factor against depression, with a 30% reduction in the prevalence of increased depressive symptoms in this group. This is consistent with the inflammatory hypothesis of depression. Obesity is closely linked to inflammation [44], making this the group of patients with potentially higher levels of inflammatory markers, in which the anti-inflammatory and antioxidant properties of statins may exert their biggest influence. Unfortunately, we do not have access to inflammatory measures, but evidence suggests that anti-inflammatory drugs tend to have a stronger antidepressant effect in patients with high inflammatory markers at baseline [45, 46]. All performed subgroup analyses are exploratory in nature and should be interpreted with caution.

In an exploratory analysis, we found that simvastatin was marginally associated with an increased prevalence of depressive symptoms. Our findings agree with a large propensity-matched score study of almost 300,000 people initiating statins in the USA [12]. This study aimed to compare the risk of depression between lipophilic and hydrophilic statins. The authors found that only simvastatin was associated with a moderate increased risk of depressive symptoms (hazard ratio 1.09, 95% CI 1.02–1.16, $p = 0.003$), although the effect size was not large [12]. Several possible mechanisms have been suggested for the association of simvastatin with depression. Simvastatin is the most lipophilic statin of all. Accordingly, it can more easily pass through the blood–brain barrier and directly influence mood [47]. Brain cholesterol is synthesised by the brain itself, with little influence from external cholesterol, and rates of brain cholesterol synthesis tend to decrease with age [47]. This high permeability might grant simvastatin an increased potential to interfere in this homeostasis, lowering brain cholesterol levels and possibly interfering with myelination processes and the development of subsequent cognitive and mood symptoms [10]. Lipophilic statins have been associated with suicidal ideation [48] and depressive symptoms in elderly populations [5].

The strengths of this study include a much larger sample of older adults than in precursor studies, a comprehensive assessment of individuals, a validated instrument for the measurement of depressive symptoms, and robust data on mental and physical conditions, which gives us a high-resolution lens to explore this relationship in an older population. Accounting for a variety of socioeconomic factors and physical conditions in well-powered multivariable models was another advantage.

There are several limitations to this study. First, owing to its design, as a cross-sectional study, only association, and not causation, can be inferred from it. Additionally, notwithstanding the fact that the CES-D 10 is a valuable tool for depression screening, it is not a formal diagnostic test for depression. The high sensitivity but suboptimal specificity of the test can increase heterogeneity in the depressed group, pushing the results towards the null hypothesis. The duration and doses of statins used may also interfere in their relationship with depression. Unfortunately, we do not have data on these aspects of statin

use from ASPREE participants. Another limitation comes from exclusion criteria. Because ASPREE is a study of a healthy old-age population, and excluded subjects with severe diseases, dementia, uncontrolled hypertension, and especially, people with a history of CVD, these subgroups were unable to be addressed in this sub-study. Cardiovascular disease has been consistently linked to inflammation and depression [31, 49] and the effects of statins in reducing mortality in this population have been strongly documented in the literature [15, 18]. In this specific population, statins may have more psychological benefits than in the individuals investigated here. Extrapolation of our results to the general population should be made with caution.

5 Conclusion

This study provides further evidence from a large and very well-characterised sample of community-dwelling older people on the controversial topic of statins and depression in this population. In conclusion, we found no association of statins with depressive symptoms after accounting for important confounding factors. Confounding by indication is a major issue in pharmacoepidemiologic studies and must be addressed thoroughly. This study however provides second-level evidence for an association of statin use and increased odds of depressive symptoms in individuals between 75 and 84 years of age and a protective effect of statins in depressive symptoms for patients with a BMI > 35 kg/m^2.

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References

1. Arokiasamy P, et al. The impact of multimorbidity on adult physical and mental health in low- and middle-income countries: what does the study on global ageing and adult health (SAGE) reveal? BMC Med. 2015;13(1):1–16. [PubMed: 25563062]
2. World Health Organization. Depression and other common mental disorders: global health estimates. Geneva: World Health Organization; 2017 p. 1–24.
3. Sirtori CR. The pharmacology of statins. Pharmacol Res. 2014;88:3–11. [PubMed: 24657242]
4. Bakunina N, Pariante CM, Zunszain PA. Immune mechanisms linked to depression via oxidative stress and neuroprogression. Immunology. 2015;144(3):365–73. [PubMed: 25580634]
5. You H, Lu W, Zhao S, Hu Z, Zhang J. The relationship between statins and depression: a review of the literature. Expert Opin Pharmacother. 2013;14(11):1467–76. [PubMed: 23767773]
6. Williams LJ, et al. Statin and aspirin use and the risk of mood disorders among men. Int J Neuropsychopharmacol. 2016;19(6):1–4.
7. Salagre E, Fernandes BS, Dodd S, Brownstein DJ, Berk M. Statins for the treatment of depression: a meta-analysis of randomized, double-blind, placebo-controlled trials. J Affect Disord. 2016;200:235–42. [PubMed: 27148902]
8. Redlich C, Berk M, Williams LJ, Sundquist J, Sundquist K, Li X. Statin use and risk of depression: a Swedish national cohort study. BMC Psychiatry. 2014;14:438.

9. Mandas A, et al. Cognitive decline and depressive symptoms in late-life are associated with statin use: evidence from a population-based study of Sardinian old people living in their own home. Neurol Res. 2014;36(3):247–54. [PubMed: 24512018]
10. Tuccori M, et al. Neuropsychiatric adverse events associated with statins: epidemiology, pathophysiology, prevention and management. CNS Drugs. 2014;28(3):249–72. [PubMed: 24435290]
11. Thompson PD, Panza G, Zaleski A, Taylor B. Statin-associated side effects. J Am Coll Cardiol. 2016;67(20):2395–410. [PubMed: 27199064]
12. Dave CV, Winterstein AG, Park H, Cook RL, Hartzema AG. Comparative risk of lipophilic and hydrophilic statins on incident depression: a retrospective cohort study. J Affect Disord. 2018;238:542–6. [PubMed: 29936394]
13. Glaus J, et al. Aspirin and statin use and the subsequent development of depression in men and women: results from a longitudinal population-based study. J Affect Disord. 2015;182:126–31. [PubMed: 25985382]
14. Bulbulia R, et al. Effects on 11-year mortality and morbidity of lowering LDL cholesterol with simvastatin for about 5 years in 20 536 high-risk individuals: a randomised controlled trial. Lancet. 2011;378(9808):2013–20. [PubMed: 22115874]
15. Collins R, et al. Interpretation of the evidence for the efficacy and safety of statin therapy. Lancet. 2016;388(10059):2532–61. [PubMed: 27616593]
16. Mortensen MB, Falk E. Primary prevention with statins in the elderly. J Am Coll Cardiol. 2018;71(1):85–94. [PubMed: 29301631]
17. Ruscica M, Macchi C, Pavanello C, Corsini A, Sahebkar A, Sirtori CR. Appropriateness of statin prescription in the elderly. Eur J Intern Med. 2018;50:33–40. [PubMed: 29310996]
18. Waters DD. Meta-analyses of statin trials: clear benefit for primary prevention in the elderly. J Am Coll Cardiol. 2013;62(22):2100–1. [PubMed: 23994398]
19. Ridker PM. Should aspirin be used for primary prevention in the post-statin era? N Engl J Med. 2018;379(16):1572–4. [PubMed: 30332575]
20. McNeil JJ, Nelson MR, Woods RL, et al. Effect of aspirin on all-cause mortality in the healthy elderly. N Engl J Med. 2018;379:1519–28. [PubMed: 30221595]
21. McNeil JJ, Wolfe R, Woods RL, et al. Effect of aspirin on cardiovascular events and bleeding in the healthy elderly. N Engl J Med. 2018;379:1509–18. [PubMed: 30221597]
22. Grimm R, et al. Study design of ASPirin in Reducing Events in the Elderly (ASPREE): a randomized, controlled trial. Contemp Clin Trials. 2013;36(2):555–64. [PubMed: 24113028]
23. Andresen EM, Malmgren JA, Carter WB, Patrick DL. Screening for depression in well older adults: evaluation of a short form of the CES-D (Center for Epidemiologic Studies Depression Scale). Am J Prev Med. 1993;10(2):77–84.
24. Vilagut G, Forero CG, Barbaglia G, Alonso J. Screening for depression in the general population with the Center for Epidemiologic Studies Depression (CES-D): a systematic review with meta-analysis. PLoS One. 2016;11(5):1–17.
25. Mohebbi M, et al. Psychometric properties of a short form of the Center for Epidemiologic Studies Depression (CES-D-10) scale for screening depressive symptoms in healthy community dwelling older adults. Gen Hosp Psychiatry. 2018;51:118–25. [PubMed: 28890280]
26. Irwin M, Artin KH, Oxman MN. Screening for depression in the older adult. Arch Intern Med. 1999;159:1701–4. [PubMed: 10448771]
27. Cheng ST, Chan ACM. The Center for Epidemiologic Studies Depression Scale in older Chinese: thresholds for long and short forms. Int J Geriatr Psychiatry. 2005;20(5):465–70. [PubMed: 15852439]
28. Alberti KGM, Zimmet P, Shaw J. The IDF consensus worldwide definition of the metabolic syndrome. Brussels Int Diabetes Fed. 2006;23(5):469–80.
29. Otte C, et al. Major depressive disorder. Nat Rev Dis Prim. 2016;2:16065. [PubMed: 27629598]
30. Delgado I, et al. Depressive symptoms in obesity: relative contribution of low-grade inflammation and metabolic health. Psychoneuroendocrinology. 2018;91:55–61. [PubMed: 29525586]

31. Cohen BE, Edmondson D, Kronish IM. State of the art review: depression, stress, anxiety, and cardiovascular disease. Am J Hypertens. 2015;28(11):1295–302. [PubMed: 25911639]
32. De Jonge P, Roy JF, Saz P, Marcos G, Lobo A. Prevalent and incident depression in community-dwelling elderly persons with diabetes mellitus: results from the ZARADEMP project. Diabetologia. 2006;49(11):2627–33. [PubMed: 17019601]
33. Bagherniya M, et al. Metabolic syndrome and its components are related to psychological disorders: a population based study. Diabetes Metab Syndr Clin Res Rev. 2017;11:S561–6.
34. Mulvahill JS, et al. Effect of metabolic syndrome on late-life depression: associations with disease severity and treatment resistance. J Am Geriatr Soc. 2017;65(12):2651–8. [PubMed: 29235659]
35. Qato DM, Ozenberger K, Olfson M. Prevalence of prescription medications with depression as a potential adverse effect among adults in the United States. JAMA. 2018;319(22):2289. [PubMed: 29896627]
36. Agustini B, Berk M. Medications with depression as an adverse effect. JAMA. 2018;320(17):1815.
37. Friis RH, Sellers TA. Experimental study designs. Epidemiol Public Health Pract. 2009;275(6): 327–60.
38. Köhler-Forsberg O, Gasse C, Petersen L, Nierenberg AA, Mors O, Østergaard SD. Statin treatment and the risk of depression. J Affect Disord. 2019;246:706–15. [PubMed: 30611914]
39. Mansi I, Frei CR, Pugh MJ, Mortensen EM. Psychologic disorders and statin use: a propensity score-matched analysis. Pharmacotherapy. 2013;33(6):615–26. [PubMed: 23625731]
40. Schaakxs R, Comijs HC, Lamers F, Kok RM, Beekman ATF, Penninx BWJH. Articles associations between age and the course of major depressive disorder: a 2-year longitudinal cohort study. Lancet Psychiatry. 2018;366(18):1–10.
41. Taylor WD, Aizenstein HJ, Alexopoulos GS. The vascular depression hypothesis: mechanisms linking vascular disease with depression. Mol Psychiatry. 2013;18(9):963–74. [PubMed: 23439482]
42. Geerlings MI, Gerritsen L. Late-life depression, hippocampal volumes, and hypothalamic-pituitary-adrenal axis regulation: a systematic review and meta-analysis. Biol Psychiatry. 2017;82(5):339–50. [PubMed: 28318491]
43. Liang Feng TPN, Yap KB, Kua E. Statin use and depressive symptoms in a prospective study of community-living older persons. Pharmacoepidemiol Drug Saf. 2010;19:942–8. [PubMed: 20575082]
44. Bornstein SR, Schuppenies A, Wong M-L, Licinio J. Approaching the shared biology of obesity and depression: the stress axis as the locus of gene–environment interactions. Mol Psychiatry. 2006;11(10):892–902. [PubMed: 16880826]
45. Raison CL, et al. A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression. JAMA Psychiatry. 2013;70(1):31–41. [PubMed: 22945416]
46. Köhler O, et al. Effect of anti-inflammatory treatment on depression, depressive symptoms, and adverse effects. JAMA Psychiatry. 2014;71(12):1381–91. [PubMed: 25322082]
47. McFarland AJ, et al. Molecular mechanisms underlying the effects of statins in the central nervous system. Int J Mol Sci. 2014;15(11):20607–37. [PubMed: 25391045]
48. Davison KM, Kaplan BJ. Lipophilic statin use and suicidal ideation in a sample of adults with mood disorders. Crisis. 2014;35(4):278–82. [PubMed: 25113893]
49. Teply RM, Packard KA, White ND, Hilleman DE, DiNicolantonio JJ. Treatment of depression in patients with concomitant cardiac disease. Prog Cardiovasc Dis. 2016;58(5):514–28. [PubMed: 26562328]

Key Points

Statin use was not significantly associated with increased depressive symptoms after adjusting for confounders.

Simvastatin, the most lipophilic statin, was marginally associated with an increased prevalence of depressive symptoms.

Statin use was associated with an increased prevalence of depressive symptoms in individuals between 75 and 84 years of age and a decreased prevalence in individuals with a body mass index > 35 kg/m^2.

Table 1

Sociodemographic characteristics: statin users vs. non-statin users

	No. of participants	Statin users: *n* (%)	Non-statin users: *n* (%)	*P*-value
Overall	19,114	5987 (31.3)	13,127(68.7)	
Sex				
Male	8331 (43.6)	2337 (39.0)	5994 (45,6)	< 0.001
Female	10,783 (56.4)	3650 (60.9)	7133 (54.3)	
Living status				
At home alone	6252 (32.7)	2001 (33.4)	4251 (32.4)	0.34
At home with someone	12,779 (66.8)	3959 (66.1)	8820 (67.2)	
In a residential home	83 (0.4)	27 (0.4)	56 (0.4)	
Education (years)				
≤ 12	10,955 (57.3)	3668 (61.3)	7287 (55.5)	< 0.001
> 12	8158 (42.7)	2319 (38.7)	5839 (44.5)	
Smoking history				
Current	735 (3.8)	238 (3.9)	497 (3.8)	0.52
Former or never	18,379 (96.2)	5749 (96.1)	12,630 (96.2)	
Age (years)				
65–70	564 (2.9)	199 (3.3)	365 (2.8)	0.001
70–75	10,599 (55.4)	3306 (55.2)	7293 (55.5)	
75–80	5023 (26.3)	1630 (27.2)	3393 (25.8)	
80–85	2196 (11.5)	664 (11.1)	1532 (11.7)	
> 85	732 (3.8)	188 (3.1)	544 (4.1)	
Body mass index (kg/m^2)				
≤ 25	5050 (26.5)	1181 (19.8)	3869 (29.6)	< 0.001
25–30	8452 (44.4)	2670 (44.8)	5782 (44.2)	
30–35	4009 (21.1)	1486 (24.9)	2523 (19.3)	
> 35	1524 (8.0)	620 (10.4)	904 (6.9)	
Blood lipid profile Total cholesterol (mg/dL)				
≤ 200	9090 (48.0)	4407 (74.37)	4683 (36.04)	< 0.001
> 200	9831 (51.2)	1519 (25.63)	8312 (63.96)	

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	No. of participants	Statin users: *n* (%)	Non-statin users: *n* (%)	*P*-value
LDL (mg/dL)				
≤ 100	5604 (30.1)	3488 (60.01)	2116 (16.53)	
> 100	13,021 (69.9)	2324 (39.99)	10,688 (83.47)	
HDL (< 45 male, < 55 female)				
Low	2828 (15.1)	1056 (18.09)	1772 (13.81)	
High	15,842 (84.9)	4781 (81.91)	11,061 (86.19)	
Triglycerides (mg/dL)				
≤ 150	14,652 (77.1)	4232 (71.5)	10,330 (79.6)	
> 150	4336 (22.9)	1688 (28.5)	2648 (20.4)	
Abdominal circumference (< 88 cm female; ≤ 102 cm male)				
Normal	8866 (46.8)	2299 (38.7)	6567 (50.5)	< 0.001
High	10,055 (53.2)	3636 (61.3)	6419 (49.5)	
CES-D 10 scores				
< 8	17,231 (90.2)	5351 (89.4)	11,880 (90.5)	0.019
≥ 8	1879 (9.8)	633 (10.6)	1246 (9.5)	
Antidepressant use				
Yes	2145 (11.2)	805 (13.5)	1340 (10.2)	< 0.001
No	16,969 (88.8)	5182 (86.5)	11,787 (89.8)	
Anti-inflammatory use				
Yes	2702 (14.4)	904 (15.1)	1798 (13.7)	0.10
No	16,412 (85.6)	5083 (84.9)	11,329 (86.3)	
Quality of life (SF-12)				
Mental Component Score	55.7 (7.12)	55.56 (7.33)	55.71 (7.03)	< 0.001[a]
Physical Component Score	48.3 (8.76)	47.6 (8.94)	48.7 (8.66)	
Comorbidities				
Diabetes mellitus	2057 (10.7)	1203 (20.9)	854 (6.5)	< 0.001
High blood pressure	14,195 (74.3)	4926 (82.3)	9269 (70.6)	< 0.001
Number of concomitant medications	3 (± 4)	4 (± 3)	2 (± 3)	< 0.001[b]

CES-D Center for Epidemiological Studies Depression Scale, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein

[a]Mean and standard deviation

[b] Median and interquartile range

Table 2

Examining the association between statin use with increased depressive symptoms (Center for Epidemiological Studies Depression Scale score ≥8)

	OR	95% confidence intervals	*p* value
Any statin	1.13	1.02–1.25	0.02
Simvastatin	1.22	1.04–1.42	0.01
Sex adjusted			
Statin	1.09	0.99–1.21	0.08
Simvastatin	1.17	1.00–1.36	0.04
Age and sex adjusted			
Statin	1.10	0.99–1.21	0.07
Simvastatin	1.17	1.00–1.37	0.04
Multivariate analysis[a]			
Statin	1.09	0.98–1.20	0.11
Simvastatin	1.16	0.99–1.35	0.05

OR odds ratio

[a]Accounting for sex (OR 1.6 for female individuals), living status (at home alone: OR 1.3 female individuals, OR 2.0 male individuals; in a residential home: OR 2.2 female individuals, OR 2.7 male individuals), education (OR 1.2, age < 12 years) and smoking history (OR 1.4 female individuals, OR 1.8 male individuals, for current smokers) (all significant at 0.05 level). Non-significant variables were excluded from multivariable models using a backward elimination method

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Table 3

Subgroup analyses on the association between statin use with depressive symptoms accounting for age, metabolic conditions and medication use

Subgroup analysis	Participants, *n* (%)	CES-D ≥ 8		MOR[a]	95% confidence intervals	*p* value
		Statin, *n* (%)	Non-statin, *n* (%)			
BMI (kg/m^2)						
≤ 25	5050 (26.5)	108 (9.1)	355 (9.2)	0.95	0.75–1.19	0.63
25–30	8452 (44.4)	278 (10.5)	503 (8.7)	1.16	0.99–1.36	0.05
30–35	4009 (21.1)	172 (11.5)	243 (9.6)	1.20	0.97–1.48	0.08
35 +	1524 (8.0)	71 (11.4)	139 (15.4)	0.69	0.51–0.95	0.02
Age (years)						
≤ 74	11,163 (58.4)	351 (10.5)	726 (9.5)	1.02	0.89–1.17	0.75
75–84	7219 (37.8)	265 (11.5)	459 (9.3)	1.21	1.04–1.43	0.01
85 +	732 (3.8)	17 (9.0)	61 (11.2)	0.82	0.47–1.45	0.51
Diabetes mellitus						
Yes	2057 (10.3)	158 (13.1)	92 (10.7)	1.23	0.93–1.62	0.14
No	17,057 (89.2)	475 (9.9)	1154 (9.4)	1.01	0.90–1.13	0.79
Hypertension						
Yes	14,195 (74.3)	524 (10.6)	890 (9.6)	1.07	0.96–1.21	0.45
No	4919 (25.7)	109 (10.3)	356 (9.2)	1.09	0.87–1.37	0.43
Abdominal circumference						
Normal	8866 (46.9)	198 (8.6)	556 (8.5)	0.98	0.83–1.17	0.89
High	10,055 (53.1)	424 (11.6)	678 (10.5)	1.08	0.95–1.23	0.22
Antidepressant use						
Yes	2145 (11.2)	174 (27.4)	282 (22.6)	1.01	0.82–1.26	0.88
No	16.969 (88.7)	459 (72.5)	964 (77.4)	1.06	0.94–1.19	0.32
Anti-inflammatory use						
Yes	2702 (14.4)	109 (12.8)	206 (11.4)	1.03	0.80–1.32	0.82
No	16,412 (85.6)	524 (10.3)	1040 (9.2)	1.10	0.98–1.22	0.10

BMI body mass index, *CES-D* Center for Epidemiological Studies Depression Scale

[a]MOR: model-adjusted odds ratio accounting for sex, living status, education and smoking history (all significant at 0.05 level). Non-significant variables were excluded from multivariable models using a backward elimination method