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Review

Statins use and risk of depression: A systematic review and meta-analysis

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ABSTRACT

Importance: Statin use has been associated with depression; however studies of the association between statin use and depression have yielded mixed results.
Objective: To determine whether statin use is associated with depression and to evaluate the evidence supporting this association.
Data sources: Ovid MEDLINE In-Process & Other Non-Indexed Citations, Ovid MEDLINE, EMBASE, PsycInfo, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Scopus were searched through December 28, 2012.
Study selection: We included studies that evaluated exposure to statins, reported the development of depression, and relative risks or odds ratios (ORs) or provided data for their estimation. Two reviewers screened 981 abstracts independently using a standardized form, reviewed full text of 59 selected articles, and included 7 studies in this metaanalysis.
Data extraction and synthesis: Study design, statin exposure, development of depression, and study quality were extracted by 2 independent reviewers. A pooled OR with 95% confidence interval (CI) was estimated using the random-effects model and heterogeneity was assessed using Cochran's Q test and the I^2 statistic.
Results: Seven observational studies (4 cohort, 2 nested case-control, and 1 cross-sectional) from 5 countries enrolling 9187 patients were included. Statin users were 32% less likely to develop depression than nonusers (adjusted OR, 0.68; 95% CI, 0.52–0.89). Modest heterogeneity was observed between the studies ($I^2=55\%$, $P=0.01$), which could be accounted for by one study, exclusion of which removed the heterogeneity ($P=0.40$, $I^2=2\%$) and further strengthened the antidepressant effect of statin (adjusted OR, 0.63; 95% CI, 0.43–0.93). Heterogeneity could not be explained by study design or study population. The quality of supporting evidence was fair.
Conclusions and relevance: This systematic review and meta-analysis suggests that statin use is associated with lower risk for depression. However, higher-quality studies are needed to confirm the magnitude of this association.

Contents

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1. Introduction

Statins (hydroxymethylglutaryl co-A reductase inhibitors) play a beneficial role in the primary and secondary prevention of coronary artery disease (CAD), including among patients with average cholesterol level (Benito-León et al., 2010; Carney and Freedland, 2008; Chan et al., 2000). Statins also have reported benefits in various other disorders including Alzheime's disease (Cochran, 1954) and other dementia, stroke, macular degeneration and osteoporosis (Cohen, 1960; Davey Smith and Pekkanen, 1992; DerSimonian and Laird, 1986; Downs et al., 1993, 1998; Engelberg, 1992; Freedman et al., 1995; Goldberg et al., 1998). This suggests that statins may have advantages beyond their effect on CAD and cholesterol. As statin use expands, concerns have been raised about possible negative consequences, including increased risk of non-cardiac death and a possible association of low serum cholesterol with antisocial personality, violent behavior, suicide, and aggressive conduct (Hall et al., 2001; Harrison and Ashton, 1994; Higgins et al., 2003; Hillbrand et al., 1995; Jick et al., 2000; Keech et al., 1994; Lindberg and Hallas, 1998; Marx, 2001). Given these concerns regarding statins and behavioral issues, several studies have attempted to determine a connection between statins and depression. A postulated mechanism for positive association of statins with depression relates to low plasma cholesterol leading to decreased membrane cholesterol in the brain, which could affect central neurotransmitter function and lower serotonergic activity, leading to depression (Harrison and Ashton, 1994). Possible direct effect of statins on brain functions could also be responsible for depression (Harrison and Ashton, 1994). Remission rates for elderly depressed patients treated with antidepressants have been shown to be lower when the same patients are taking cholesterol lowering medications (McAlister et al., 2001). This evidence further supports the positive association between the use of statins and depression.

On the other hand, protective effect of statins against depression has also been reported (Meier et al., 2000; Moher et al., 2009). In addition, several studies report no association between depression and statins (Muldoon, 1994; Muldoon et al., 1990; O'Neil et al., 2012; Oliver, 1992; Otte et al., 2012; Pasco et al., 2010). Thus, the association of statins with depression has remained uncertain. A recent review by While et al. found conflicting evidence for the association of statins with mood, however they could not reach a definite conclusion and they did not perform a meta-analysis (Pedersen et al., 1996).

Therefore, we performed a systematic review and meta-analysis of all studies evaluating the association between statin use and depression, to quantify the magnitude of this association and appraise the quality of the supporting evidence.

2. Methods

This systematic review and meta-analysis is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) stat0ement guidelines (Sacks et al., 1996).

2.1. Study eligibility

We included comparative studies of any design (randomized control trials, cohort, case control and cross-sectional). Eligible studies had to provide documentation of statin use, measure depression as a predefined outcome of interest, and report risk estimates or frequency data from which one could calculate the risk estimates for depression with statin use. Inclusion was not restricted by language or publication status. When data were reported from overlapping study samples (e.g., multiple publications from the same study), data were included from most recent comprehensive report. Studies reporting depression as a post hoc outcome were excluded because of the risk of potential bias due to non-adjustment for confounders.

2.1.1. Data sources and search

A comprehensive search strategy was designed with the assistance of an expert librarian. Major data bases including Ovid MEDLINE In-Process & Other Non-Indexed Citations, Ovid MEDLINE, EMBASE, PsycInfo, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Scopus were searched on December 28, 2012. The complete search strategy is available in Appendix A. We had searched the references cited in the potentially eligible articles and conference proceedings of major psychiatry, internal medicine, cardiovascular and pharmacology organizations. Full articles of relevant abstracts were searched in the PubMed to further increase the yield of relevant articles.

2.1.2. Study selection

Two reviewers (AKP and BS) screened all titles and abstracts independently using a standardized form. This was followed by full text review of selected articles by the same two reviewers. We assessed interobserver agreement on study selection by Cohen's κ (Sano et al., 2011), and resolved disagreements by consensus in the presence of 3rd reviewer.

2.2. Data extraction

Two reviewers (AKP, BS) extracted data independently from selected studies using a predesigned form. Authors of original studies were contacted to obtain missing data whenever required.

The following data were extracted: study characteristics (author, country, study design, study population, number of participants, and conclusion), exposure data (type of statins) and outcome data (scale used to measure depression and risk estimate for depression). Whenever multiple models for risk estimates were reported, we collected the most fully adjusted risk estimates. Disagreements in data extraction were resolved by consensus. When cohort studies reported both cross sectional and longitudinal models, we used risk estimates from the longitudinal models.

2.3. Quality assessment

The methodologic quality assessment of the included studies was performed by two investigators (AKP, BS) in parallel. Disagreements were resolved by discussion and consensus in the presence of third reviewer. Studies were assessed for risk of bias in selection (4 questions), comparability of study groups (2 questions), and ascertainment.

of the outcome of interest (3 questions). Cohort studies were assessed using the Newcastle–Ottawa Quality Assessment Scale for cohort studies, and case-control and cross-sectional studies were assessed using the Newcastle–Ottawa Scale modified for case-control studies (Santos et al., 2012).

2.4. Outcome assessment

Our primary analysis was to evaluate the risk of depression associated with statin use.

A priori analyses were planned to explain the potential heterogeneity in the direction and magnitude of the effect estimate among different studies. These analyses evaluated the effect of study design [longitudinal (case-control and cohort) vs. cross-sectional and cohort vs. others] and study population [patients with coronary artery disease (CAD) vs. patients without CAD], given that depression is high in patients with CAD (Scandinavian Simvastatin Survival Study Group, 1994) with statin being the commonly used drug.

2.5. Data synthesis and analysis

All studies reported adjusted OR except for one study reporting RR, which was converted into OR using a standard formula (Scott and Laake, 2001). We recorded continuous variables as means with standard deviation (SD) or medians with interquartile range (IQR), and categorical variables as frequency and proportions. The DerSimonian and Laird random effects model was used to generate the pooled OR for depression associated with statin use (Stafford and Berk, 2011). We evaluated heterogeneity across the included studies using the I^2 statistic and Cochran's Q test (Steffens et al., 2003). Substantial heterogeneity that is due to real differences in the study population, methodology and outcome is indicated by an I^2 value $>50\%$ and a small p value (<0.10) of the Cochran's Q test, both suggesting that the observed heterogeneity is beyond that expected due to random error (Sterne et al., 2000). All statistical analyses were performed using Review Manager (RevMan) Version 5.1 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011).

3. Results

3.1. Study selection

The initial search identified 979 articles; two additional articles were identified through the references search of relevant articles. No additional articles were identified from the search of conference proceedings. Preliminary screening of titles and abstracts excluded 922 articles (Fig. 1) with an interobserver agreement of kappa=0.94 (95% CI 0.89–0.98). Full text review of the remaining 59 articles was done by same two reviewers in parallel, resulting in inclusion of 7 studies in the final analysis (kappa=0.86, 95% CI 0.71–1.00). Reasons for excluding the studies are reported in Fig. 1. Three authors were contacted for desirable/missing data, and two provided the required data (McAlister et al., 2001; Virkkunen and Penttinen, 1984).

3.2. Characteristics of included studies and qualitative summary

A detailed description of the included 7 studies is presented in Supplementary Table 1. All studies were observational designs, including four cohort studies (2 USA, 1 Australia, 1 Denmark), one cross-sectional study (Singapore), and two nested case-control

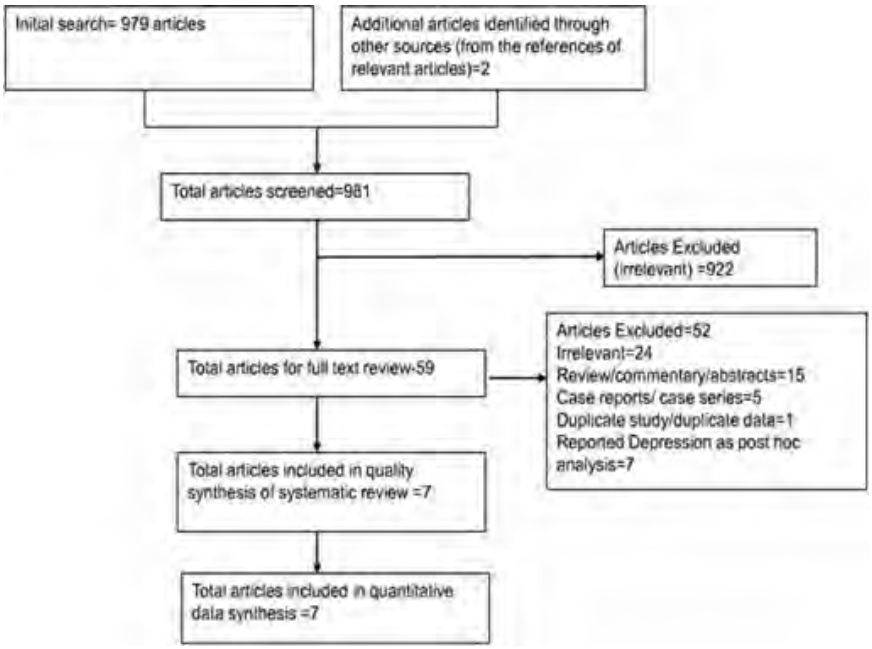

Fig. 1. Flow diagram for the selection of references.

studies (1 UK, 1 Australia). Sample size ranged from 193 to 2288 (total 9187) participants, with 37% males. The mean age of participants was 64.0 ± 5.0 years. Study populations differed across the studies and are described in Supplementary Table 1. A detailed quality assessment of the included studies is reported in Supplementary Table 1A and B. All studies scored fairly on the appropriate quality assessment tool. Agreement between the reviewers was high on each item of the Newcastle–Ottawa scale (> 90%). The median follow-up period for the 4 prospective cohort studies was 4 years (IQR 1.6–4 years) (O'Neil et al., 2012; Virkkunen and Penttinen, 1984; Wang et al., 2000; Wardle et al., 1996).

3.3. Meta-analysis

The overall pooled OR for depression among statins users was 0.68 (95% confidence interval 0.52–0.89), consistent with a protective effect of statins against depression. However, modest heterogeneity was observed between the studies (Cochran's Q test $P=0.014$, $I^2=55\%$) (Fig. 2).

Subgroup analysis (Fig. 3A, B and C) by study design (longitudinal vs. cross-sectional and cohort vs. other) and study population (studies including patients with CAD vs. patients without CAD), did not demonstrate a significant interaction to explain heterogeneity ($P=0.71$, 0. 21 and 0.41 respectively).

To further explore potential sources of the modest heterogeneity observed in this analysis, we excluded each study sequentially to determine its effect on the main summary estimate. After removing the Lindberg and Hallas (1998) study, the pooled OR decreased slightly to 0.63 (95% confidence interval 0.43–0.93), now with no significant heterogeneity (Cochran's Q test $P=0.40$, $I^2=2\%$). This study enrolled only patients who were taking statins and antidepressants both during the study period, and those who started the statins before antidepressants were considered to have statin-induced depression. Such approach may introduce selection bias and produce confounding by indication, which may have increased its risk estimate.

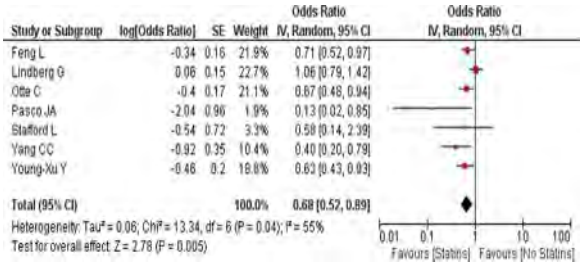

Fig. 2. Association of statins with depression.

4. Discussion

This meta-analysis based on a systematic review of current evidence drawn from seven observational studies with good quality enrolling 9187 participants suggests that statins have a protective effect against depression. These studies were conducted in diverse populations across multiple countries making the results more generalizable.

Our findings are consistent with a previous meta-analysis of clinical trials that evaluated the impact of statins on psychosocial wellbeing (Wells Gas et al., 2013), although that study focused on mood scores of statin users and not on patients meeting diagnostic criteria for depression. They compared the mood score of all subjects with or without depression and found higher score among statin users.

Possible underlying mechanism of antidepressant effect of statins may be its ability to reduce oxidative stress and inflammatory cytokines which appear to play an etiological role in the genesis of depression (Goldberg et al., 1998). Neuroprotective

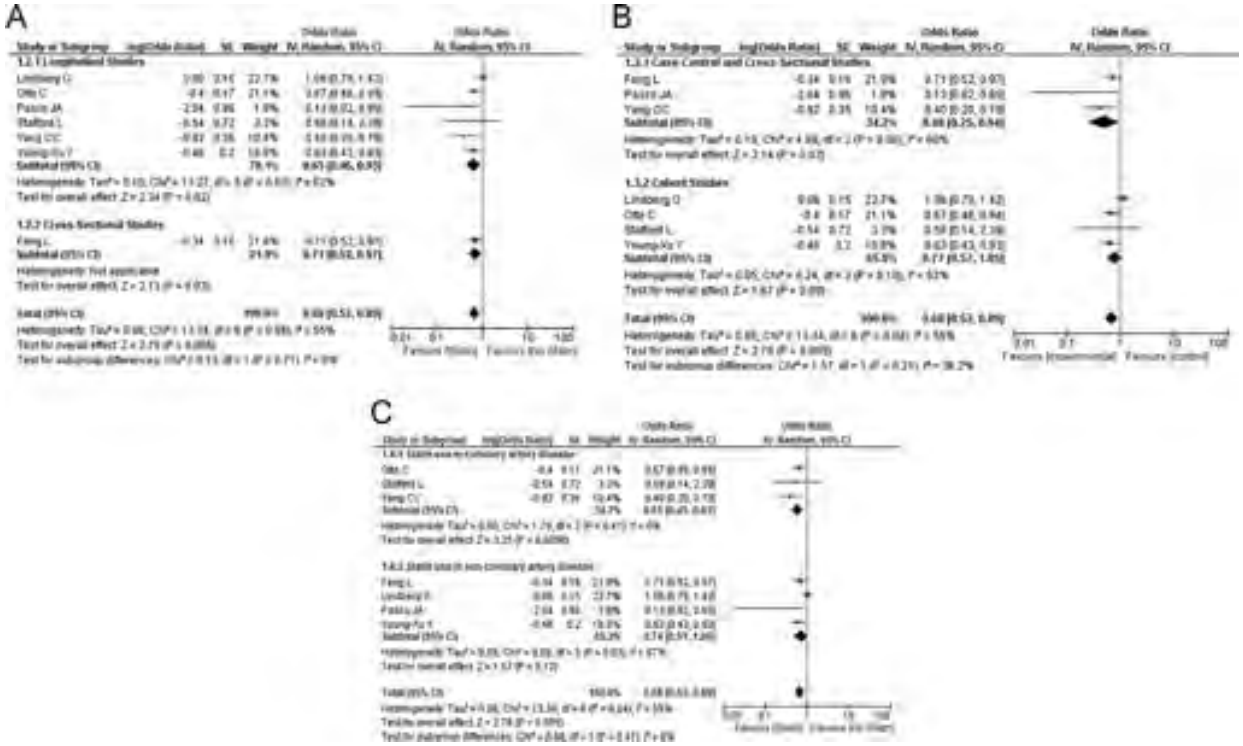

Fig. 3. Subgroup analysis between (A) longitudinal vs. cross-sectional studies, (B) cohort vs. other studies (case-control and cross sectional studies) and (C) coronary artery disease vs. non coronary artery disease.

effects of statins are also attributed to its effect on immune system and improved blood-flow in addition to reduced oxidative damage (While and Keen, 2012). Antidepressant effects of statins have been also been supported in animal studies (Wolozin et al., 2000). Other possible reason for beneficial effects of statins against depression, especially among patients with underlying cardiovascular disorders could be decreased cardiovascular events, more health consciousness and treatment compliance among statins users, which can improve the quality of life, eventually decreasing the risk of depression (Pasco et al., 2010; Yang et al., 2003).

Modest heterogeneity seen in overall results was the effect of one study (Lindberg et al.), in which study population was subjects using statins and antidepressants both during the study period (O'Neil et al., 2012). After the post hoc exclusion of this study from analysis, we observed significant homogeneity between the studies with further strengthening of anti-depression effect of statins. Therefore the variability in the methodology of this study may have overestimated the depression risk associated with statins use. Our findings shed light on the importance of methodological issues that has limited the inferences from the studies with different methodological approaches and were excluded from our meta-analysis (studies comparing depression score between statins user vs. non-users without comparing the true depression cases, and studies reporting depression as a post hoc outcome without adjustment for confounders). Seven studies were excluded during the study selection after full text review because they reported depression as post hoc outcome, of which one study reported borderline negative association between statin use and depression (McAlister et al., 2001), while others reported no association (Muldoon, 1994; Muldoon et al., 1990; Oliver, 1992; Otte et al., 2012; Young-Xu et al., 2003; Zhang and Yu, 1998).

This study has few limitations common to meta-analyses. We used aggregated data from all studies as individual data were unavailable, and therefore could not account for patient-level characteristics. A second limitation is that adjustment for confounders varied across the studies. All studies used different scales for reporting depression, few of which may not be as reliable as standard diagnostic criteria. Also, the familiarity with the study objectives of two reviewers involved in study selection may have caused some bias. However, it is customary in systematic reviews to review and select studies in duplicates, where the blinding of reviewers is not practical and not commonly done. Finally, the publication bias could not be tested, because the tests for publication bias are unreliable when the number of studies is <20 in meta-analysis (van der Most et al., 2009). Strengths of this systematic review and meta-analysis include the exhaustive literature search strategy and bias protection measures (study selection and quality assessment done in duplicate with good interviewer agreement), subgroup analysis and the good methodological quality of most of the included studies. We used random effects model for analysis, which take into account the presence of between-study heterogeneity.

In summary, this meta-analysis suggests that statin users are less likely to develop depression compared to statin nonusers. However, higher-quality studies are needed to confirm the magnitude of this association.

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Conflict of interest

None of the authors have any conflict of interest.

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Ajay K. Parsaik has full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.jad.2013.11.026.

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