

Accepted Manuscript

Do Statins have an Effect on Depressive Symptoms? A Systematic Review and Meta-Analysis

Megha Sai Yatham BSc , Kavya Sai Yatham BSc ,
Arun V Ravindran MDFRCPC ,
Frank Sullivan FRSE,FRCP, FRCGP

PII: S0165-0327(19)30975-9
DOI: <https://doi.org/10.1016/j.jad.2019.07.002>
Reference: JAD 10919



To appear in: *Journal of Affective Disorders*

Received date: 15 April 2019
Revised date: 28 June 2019
Accepted date: 1 July 2019

Please cite this article as: Megha Sai Yatham BSc , Kavya Sai Yatham BSc , Arun V Ravindran MDFRCPC , Frank Sullivan FRSE,FRCP, FRCGP , Do Statins have an Effect on Depressive Symptoms? A Systematic Review and Meta-Analysis, *Journal of Affective Disorders* (2019), doi: <https://doi.org/10.1016/j.jad.2019.07.002>

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Highlights

- Statins are effective in improving depressive symptom scores in clinically depressed population
- Statins do not induce depressive symptoms in non-depressed populations
- Statin use is associated with numerically lower depressive symptom scores in clinically non-depressed population compared with placebo use

ACCEPTED MANUSCRIPT

Do Statins have an Effect on Depressive Symptoms? A Systematic Review and Meta-Analysis

Megha Sai Yatham¹ BSc, Kavya Sai Yatham² BSc, Arun V Ravindran³,MD, FRCPC, Frank Sullivan⁴ FRSE,FRCP, FRCGP,

¹Manchester Royal Infirmary, University of Manchester, Manchester

²St. Georges University of London, London. UK

³Department of Psychiatry, University of Toronto & Centre for Addiction and Mental Health, Toronto

⁴ Division of Population and Behavioural Sciences, Medical School. University of St Andrews, Scotland.

Corresponding Author

Megha S. Yatham
University of Manchester
Oxford Road
Manchester
M13 9PL

Email: megha.yatham@student.manchester.ac.uk

ABSTRACT

Background: Clinical trials of the effects of statins in people with and without depressive symptoms at baseline have yielded conflicting results with studies reporting both an increase and decrease in depressive symptoms. To address these inconsistencies, a systematic review and meta-analysis has been conducted to determine the effects of statins on depression in those with or without clinical major depression.

Methods: A comprehensive literature search was conducted in MEDLINE, EMBASE and PsychINFO to identify relevant articles that met predefined inclusion and exclusion criteria. The primary outcome measure was the mean difference in depression scores at endpoint between the statin and placebo groups which was computed using random effects model.

Results: 10 articles were found and used to determine the effects of statins on depressive symptoms. Subgroup analyses were performed to determine the effects of statins in patients with and without depression at baseline. Overall, statin use was associated with significantly lower scores on depression rating scales compared with the placebo use (SMD -0.309, CI: -0.525, -0.094; $p=0.005$). The subgroup analysis showed significant effects in the depressed population (SMD: -0.796, CI: -1.107, -0.486, $p=0.001$) but not in the non-depressed population (SMD: -0.153, CI -0.353, 0.047, $p=0.113$).

Limitations: There was high heterogeneity in the studies included and only two studies had low risk of bias.

Conclusion: The results suggest that statins are effective in improving depressive symptoms, particularly in those with clinical depression and that they do not worsen depression in non-depressed subjects.

Key words: Statins; Depression; Systematic review; Meta-analysis; Non depressed;

Introduction

Depressive disorders are common and can affect anyone and at any age. World Health Organization (WHO) estimates suggest that depression affects more than 300 million people of all ages globally (*WHO | Depression, 2017*). While the estimates of prevalence of major depressive disorder vary, a recent epidemiological study showed that the 12-month prevalence of DSM.5 (APA, 2013) major depressive disorder (MDD) is 10.4% and lifetime prevalence is 20.6% (Hasin *et al.*, 2018)

Depressive disorders are commonly treated with antidepressant medications or psychological treatments or their combination. It is estimated that about a third of patients with MDD exhibit some degree of refractoriness to these treatment strategies (Rush *et al.*, 2006); augmentation with atypical antipsychotics or ECT or other somatic agents are effective in improving only a proportion of such patients.

Hence, there is a continued search for newer treatments for managing patients with refractory depression; one potential option based on neurobiological data is to target inflammation. This strategy is based on several lines of evidence that suggest a significant relationship between inflammation and depression: First, depression is observed more commonly in those with inflammatory diseases (Benros *et al.*, 2013); Second, elevated levels of C reactive protein, interleukin (IL)-6, tumor necrosis factor alpha (TNF- α) and IL-1 receptor antagonist have been reported in people with depression compared with healthy controls (Liu., *et al.* 2012); Third, there is evidence that infusions of Interferon α and cytokines induce depressive symptoms (Sarkar and Schaefer., 2014). These observations have led to the inflammatory theory of

depression and the trials of anti-inflammatory interventions such as nonsteroidal anti-inflammatory agents (NSAIDs), minocycline, n-acetylcysteine, and monoclonal antibodies as possible treatments for depression. Indeed, a recent meta-analysis supports the notion that anti-inflammatory agents are effective in treating depressive symptoms (Hussain *et al.*, 2017).

Statins have been considered as a potential treatment for depression due to their strong anti-inflammatory properties (Devaraj, *et al.* 2007).. Statins have been reported to reduce C-reactive protein levels, inhibit monocyte expression of pro-inflammatory cytokines and inhibit lymphocytes by blocking leukocyte function antigen-1(LFA-1). These drugs are widely used in primary and secondary prevention of cardiovascular disease and they are in general very well tolerated. Several studies have examined the relationship between statin use and depression using various designs. A meta-analysis of observational studies reported that the likelihood of depression was 32% lower in statin users compared to those who were not taking statins (Parsaik *et al.*, 2014). A large Swedish cohort study of over 4.5 million people also showed that statin users were 5%-8% less likely to develop depression compared with those who were not taking statins (Redlich *et al.*, 2014). Further, a more recent study reported that use of statins in association with selective serotonin re-uptake inhibitors (SSRIs) was associated with 36% lower risk of hospitalization for depression compared with the use of SSRIs only (Köhler *et al.*, 2016).

The effects of statins on depression have also been examined in randomized placebo controlled trials (RCTs) in people without clinical depression at baseline. In contrast to observational studies, these trials have reported conflicting findings with some studies suggesting that statins may increase the risk of depressive symptoms (Hyypä *et al.*, 2003; Morales *et al.*, 2006) while

others reported a reduction in depressive symptoms with statin use (Ormiston *et al.*, 2003; Sparks *et al.*, 2005). Given the conflicting findings, a systematic review and meta-analysis was conducted in 2012 to address this controversy (O'Neil *et al.*, 2012). This meta-analysis included seven randomized placebo control trials (pooled total of 2105 subjects) with participants that were either healthy or had documented medical conditions (history of cardiovascular disease, hypercholesterolemia etc.) and concluded that there were neither benefits nor adverse effects on the primary outcome of psychological well-being or a secondary outcome of depression. However, the statin use was associated with significant improvements in profile of mood states scores relative to placebo (O'Neil *et al.*, 2012) but this was based on data from only 2 of the studies. Since these results are only partly consistent with observational studies, the authors suggested that further larger clinical trials are needed to assess the effects of statins on depression.

The efficacy of statins was also assessed in patients with clinical depression in randomized controlled trials (Ghanizadeh and Hedayati., 2013) (Haghighi *et al.*, 2014). (Gougol *et al.*, 2015). Statins were used as adjunctive therapy to SSRIs in these trials these trials, whose duration varied from 6 to 12 weeks. A systematic review and meta-analysis that included these 3 randomized placebo controlled trials showed that statin add-on therapy to antidepressants was effective in improving depressive symptoms as indicated by significant reduction in depressive symptoms on the Hamilton Depression rating scale score (Standardized Mean Difference: -0.73; CI; -1.04, -0.42; $p < 0.001$) (Salagre *et al.*, 2016).

Thus, the systematic reviews published to date have suggested that statin use in those that are not clinically depressed may not have a beneficial effect on psychological well-being while in those that are clinically depressed, statin adjunctive therapy is effective. The failure to show beneficial effects of statins on depression in clinical trials of non-depressed population conflicts with the data from observational studies which showed clear benefits in reducing the incidence of depression.

“Given these conflicting data, the objective for the current study was to conduct a comprehensive systematic review and meta-analysis by combining data from all relevant randomized double blind placebo controlled trials that evaluated the effects of statins on depressive symptoms in both depressed and non-depressed populations. We have also conducted a sub-group analysis to determine the effect of statins in those depressed at baseline in the trials depressed and the non-depressed study participants”.

Materials and Methods

Search strategy

Boolean terms “statin*”, “depress*” and “controlled trial” were used for search in MEDLINE, EMBASE and PsychINFO from inception to January 2, 2019 by two independent reviewers (MSY and KSY) to identify relevant articles. Any discrepancies were discussed and reviewed with the third researcher (AVR) and resolved. Both MeSh terms and keywords were used to cover subject heading as well as appearances in titles or abstracts in all databases. The full details of the search strategy can be found in supplemental figure 1. To tailor results, pre-specified search filters for randomized controlled trials were applied and these filters can be found in

supplemental figure 1. These searches yielded over 400 results; to these, search limits were applied to exclude any obvious papers that did not answer the study question or would not be suitable for analysis such as those which were not full text articles or papers not in English.

Inclusion and exclusion criteria

The inclusion and exclusion criteria for the studies were as follows:

- (1) Inclusion of subjects 18 years or older
- (2) studies were randomized double blind controlled trials of a statin (or multiple statins) vs a placebo
- (3) studies that collected data on depressive symptoms at the end of study irrespective of whether they were depressed or not at study entry
- (4) studies that reported mean or medians and standard deviations for depressive symptoms on a rating scale at the end of the study
- (5) depressive symptoms were rated on a depression rating scale eg. Hamilton Depression rating scale (Hamilton, 1960), Beck Depression inventory (Beck, et al., 1961), Geriatric Depression scale (Yesavage, et al., 1982) etc.

Any duplicate papers, or papers not in English were excluded.

The full texts of the articles were reviewed in detail to assess if they met the inclusion criteria. Further, the bibliography of these papers was reviewed to check for any additional missing studies from the original search but none were found. The studies that met the inclusion and exclusion criteria were critically appraised prior to the data extraction.

Data extraction and Primary Outcome Measure

To extract all relevant data, the standard form from the Cochrane handbook was used as a guide. The following key pieces of information were extracted for each study: the study design, study duration, sequence generation, allocation concealment, blinding, information of participants (diagnostic criteria, age, sex), intervention groups, primary outcomes of the paper, and results. For results, specifically, in order to complete the meta-analysis, the same category of data was extracted as described below.

The primary outcome measure was the mean difference in end of trial depression scores between the statin and placebo groups. To compute this, the mean depression rating scale score and standard deviation at the end of the study for both the statin and placebo groups from each study were extracted. These values were compared between the statins and placebo groups to compute the standardized mean differences in order to estimate the effect of statins on depressive symptoms. If any publications did not report endpoint data, the first author of the study was contacted in order to obtain the data. Any papers where endpoint data was unobtainable were excluded from the meta-analysis.

Risk of bias assessment

The Cochrane Collaboration's tool was used to assess risk of bias (Higgins, et al., 2011). The Form 8.5 a covers potential sources of bias including selection bias (random sequence generation, allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data) and

reporting bias (selective reporting). For each study, each category was assigned either a low risk (green), unclear risk (yellow) or high risk of bias (red). Attrition bias was allocated low risk if the dropout rate was less than 20% due to low numbers of participants in each of the studies. For assessing reporting bias, the protocols for each article was searched on clinicaltrials.gov and biomedcentral.com (BMC).

Statistical analysis

To evaluate the data that were extracted from the trials, a meta-analysis was conducted. The analysis assessed all the articles included in this review. A subgroup analysis was also performed between two different groups of participants included in this review. The first group included participants with baseline depressive symptoms. In these studies, participants were diagnosed with major depressive disorder based on Diagnostic and Statistical Manual of Mental Disorders criteria and they had a Hamilton Depression rating score (HDRS) of 22 or greater. The second subgroup was the non-depressed population composed of “healthy” participants or those with other medical conditions such as multiple sclerosis or mild brain trauma etc. These studies used various rating scales to gauge level of depressive symptoms experienced by the participants at baseline and at the end of the study. For the analysis, the mean and standard deviation of depressive symptoms at the end of the study at the final follow up were compared. In trials that included more than one statin or different doses of the same statin, the data for the statin and dose which was most comparable to the other included trials using that statin e.g. Atorvastatin 20mg was chosen for inclusion in the meta-analysis.

The meta-analysis was performed using the Comprehensive Meta-Analysis software version 2.0 (Biostat, Englewood, NJ, USA). A random effects model was used to estimate the standardized mean difference in depression scores between the statin group and placebo group. The same model was used for subgroup analysis to assess the effects of statins in depressed and non-depressed populations. A sensitivity analysis was conducted by removing one study at a time iteratively to ensure that the overall results of this meta-analysis were not driven by any one study. A Q statistic was computed to test for heterogeneity and an I^2 was estimated to quantify the magnitude of heterogeneity. Publication bias was assessed with the funnel plot test and Eggers regression intercept. The classic fail safe test was also run to estimate the number of missing studies needed to alter the results.

Results

The search strategy yielded a total of 155 papers were found (85 from MEDLINE, 59 from EMBASE, 11 from PsychINFO) After reviewing the title and abstracts of these 155 articles, 19 articles were found to match all the inclusion criteria.

This left a total of 10 papers which were included in the meta-analysis (See PRISMA flow chart in Figure 1). (Harrison and Ashton, 1994; Gengo, *et al.*, 1995; Wardle, *et al.*, 1996; Muldoon, *et al.*, 2000; Stewart, *et al.*, 2000; Ghanizadeh and Hedayati, 2013; Haghighi, *et al.*, 2014; Gougol, *et al.*, 2015; Chan, *et al.*, 2017; Robertson, *et al.*, 2017).

Of the 10 papers included, three of the articles were trials conducted on participants diagnosed with clinical depression. Seven of the articles were trials of non-depressed participants. All trials were randomized double blind placebo controlled trials, with two being crossover studies. The

study lengths varied between four weeks to four years. The trials which assessed the efficacy of statins in depressed patients had on average a much shorter trial duration (6-12 weeks) while the trials of statins in healthy subjects, and in those with medical conditions were much longer and some had follow-up periods up to four years in duration. The statins were used in trials of depressed populations as an add-on therapy to antidepressants such as citalopram or fluoxetine. Four different statins were used across the ten studies and these included atorvastatin, simvastatin, pravastatin, and lovastatin. A summary of the included papers can be seen in table 1.

Assessment of Bias

For each area of potential bias, the articles were allocated a low (green), unknown (yellow) or high (red) risk of bias (Supplemental figure 2). Three studies were assigned a low risk of bias (Haghighi, *et al.*, 2014; Gougol, *et al.*, 2015; Chan, *et al.*, 2017). These papers included detailed descriptions of randomization, allocation concealment, and how both the participants and personnel were blinded. Several other studies were assigned unclear risks due to the lack of explanation of randomization method, blinding methods etc. Out of the 10 studies, only two did not have a selective reporting bias (Chan, *et al.*, 2017; Robertson, *et al.*, 2017).

Effect of statins on depression

The primary analysis included a total of 10 studies that had a total sample size of 2,517, of which 1,348 received statins and 1,169 received placebo. A random effects analysis was conducted to compute a standardized mean difference (SMD) between the two groups. This analysis showed

that statins were significantly more effective than placebo in reducing depressive symptoms (SMD= -0.309; 95% CI: -0.525, -0.094; P=0.005) (Figure 2).

A subgroup analysis showed that statins were effective in the depressed population (SMD=-0.796; 95% CI: -1.107, -0.486; p=0.0001). In the non-depressed population, statins group had numerically greater reduction in depressive symptoms but the difference was not significant statistically (SMD=-0.153; 95% CI: -0.353, 0.047; P=0.13) (Figure 3).

The results of the iterative leave-one-study out sensitivity analysis are displayed in supplementary figure 3 in supplementary materials. The point estimates for standardized mean difference remained stable and significant indicating that no one study unduly influenced the overall results of this meta-analysis.

The observed statistical heterogeneity as indicated by the Q value ($q=35.81$; $p=0.0001$) was significant. The I^2 which was computed to quantify the magnitude of heterogeneity was high, ($I^2=74.86$) suggesting moderate to high heterogeneity, hence a random effects model was used in this meta-analysis to account for the heterogeneity between the studies included. A classic fail safe analysis was also completed which indicated that 54 studies with null results would be needed in order to make the main finding of this meta-analysis insignificant. Inspection of funnel plot (see supplementary figure 4) showed slight asymmetry but this is to be expected given the heterogeneity in studies included in this meta-analysis. The results of an Eggers regression

suggested that there was no publication bias (intercept= -1.786; 95% CI -4.08, 0.50, p-value 0.11).

Discussion

The main finding of this analysis is that statin use is associated with significantly lower depressive symptom scores compared with placebo. This suggests that statins are effective in improving depressive symptoms. This refutes the results of some clinical trials which reported that statins cause depressive symptoms or adverse effects on psychological well-being. Further, a subgroup analysis showed that statins were effective in reducing depressive symptoms in those with major depression. In subjects without depression, reduction in depressive symptoms was numerically greater in the statins group, but this difference was not significant. This suggests that statins at the very least do not worsen depressive symptoms in those without clinical depression.

Several studies in this meta-analysis did not collect baseline depression scores as they included non-depressed populations. Hence, the endpoint depression scores rather than the mean change scores in each trial were used to estimate the mean differences between the groups. Thus, it could be argued that any baseline differences in the severity of depressive symptoms may have created a bias in the estimate of the treatment effect. However, randomization to different arms at baseline would have significantly reduced this bias as the treatment and control groups were balanced in terms of clinical characteristics. An Analysis of Covariance (ANCOVA) with baseline depressive symptoms scores as a covariate would have removed the effects of any potential differences in baseline depressive symptom scores, but these were available for patients in only a few studies.

There was a statistically significant heterogeneity as indicated by significant Q statistic and high I^2 . However, this was to be expected, as the studies included consisted of two distinct study populations (depressed and non-depressed participants). Furthermore, some of the non-depressed participants included subjects with other medical conditions such as multiple sclerosis and mild traumatic brain injury. The studies also varied in terms of the ages of included participants, duration of trials, and were conducted in different regions of the world. Such heterogeneity is expected to result in differences in magnitude of benefit with treatments. Hence, a random effects model was used to account for such heterogeneity in calculating the standardized mean differences between the groups.

Given the heterogeneity in the studies included, it is important to ensure that the main finding of the current study (i.e. that statins are more effective than placebo) is not driven by the results of any one study. Reassuringly, the iterative sensitivity analysis which removed one study at a time to assess the impact of each study on overall finding, showed that the standardized mean difference in favour of statins remained stable and significant, indicating that no one study accounted for the overall findings of this meta-analysis.

The data was also evaluated for any impact of publication bias, and found such was unlikely. Although the funnel plot showed slight asymmetry, the results of Eggers regression (intercept = -1.786; 95% CI -4.08, 0.50, $p = 0.11$), indicated a low risk of publication bias. Furthermore, the classic fail safe test showed that 54 missing studies with an effect size equal to zero would be needed to render the observed result insignificant, making such less plausible.

The finding that statins are effective in improving depressive symptoms is consistent with the results of a meta-analysis of observational studies which indicated lower incidence of depression in statin users compared with general population that are not taking statins (Parsaik, *et al.*, 2014). These results are also consistent with that of a large cohort study which indicated a 5%-8% lower risk of depression in those using statins compared with those not taking statins (Redlich, *et al.*, 2014).

The findings of the current investigation are consistent with that of a previous meta-analysis which examined the effect of statins on depressive symptoms in patients with clinical depression (Salagre, *et al.*, 2016). That analysis included a total of 165 patients (statins n=82; placebo n=83) from three randomized double blind placebo controlled trials of between 6 weeks to 12 weeks in duration. Their data suggested a standardized mean difference of -0.73 (CI: -1.05, -0.41) in favour of statins suggesting that statins are significantly more effective than placebo in improving depressive symptoms when used as an adjuvant therapy to antidepressants in persons with moderate to severe depression. While the overall findings are consistent, the magnitude of effect size for statins was lower (SMD: -0.309, CI: -0.525, -0.094) in the current meta-analysis. This is likely to be because this meta-analysis included data from studies of both depressed and non-depressed populations. Indeed, a sub-analysis assessing the effect of statins in the depressed subgroup showed a SMD of -0.796 (CI: -1.107, -0.486) which is similar to the magnitude of benefit observed with statins in the previous report (Salagre, *et al.*, 2016). Thus, these results clearly confirm the findings of the previous meta-analysis which suggested that statin adjunctive therapy is effective in improving depressive symptoms in patients with moderate to severe

depression. One important caveat with the statin trials in depressed population is that all three published trials to date were conducted in one country. Although a study conducted in Korea which assessed the effects of statins given in conjunction with antidepressants on depression in patients with acute coronary syndrome suggested that more patients improved in the statin and antidepressant group compared with the no medication group, this study did not randomize subjects to statins or no medication (Kim, *et al.*, 2015). Thus, although the study results of Kim and colleagues is supportive, it cannot be taken as a confirmatory evidence. Therefore, it may be prudent to wait for replication of these findings in depressed populations from other countries before firm conclusions are drawn.

Although the main finding of current meta-analysis suggests that statins are effective in improving depression, a subgroup analysis did not demonstrate significant benefit of statins in non-depressed populations. This latter finding is consistent with a previous meta-analysis which examined the impact of statins on psychological well-being in healthy subjects and in those with other medical conditions such as history of cardiovascular disease, Alzheimer's disease etc. (O'Neil, *et al.*, 2012). That meta-analysis included seven randomized controlled trials with a pooled sample of 2,105 participants (statins n= 1,133; placebo n= 972). A test for overall effect showed that the standardized mean difference between the two groups was -0.08 (95% CI: -0.29, 0.12) which was not significant. Based on this, O'Neil and colleagues concluded that statins had neither a positive nor adverse effect on overall psychological well-being. However, it must be remembered that although statins were not significantly more effective than placebo in improving depression in non-depressed subjects, statin use was associated with numerically lower depression scores compared with the placebo use in the current investigation. This raises

the question as to whether a lack of significant benefit in the non-depressed population might be due to a “floor effect”; that is if these patients had very few if any depressive symptoms to begin with, there is not that much room for significant improvement in symptoms. Further, unlike the studies of depressed populations all of which used standard rating scales for depression, the studies in non-depressed populations used a variety of scales to measure mood symptoms which may have impacted the results. Indeed, a separate analysis conducted by O’Neill and colleagues of those studies that reported specifically mood outcomes using profile of mood states scale showed that statins were associated with significant improvements in mood scores (O’Neil, *et al.*, 2012). However, this latter analysis was based on the results of only two studies and hence caution is needed in interpreting these findings. Overall though, while there is no firm evidence yet that statins improve depressive symptoms in non-depressed populations, the evidence is sufficiently strong to indicate that at the very least, statins do not induce depressive symptoms or have adverse effects on psychological well-being.

Although the exact mechanisms by which statins might improve depressive symptoms is unknown, the leading theory is that statins decrease the inflammation and oxidative stress reported to be commonly associated with depression. As previously stated, patients with clinical depression have elevated levels of C reactive protein, interleukin (IL)-6, tumor necrosis factor alpha (TNF- α) and IL-1 receptor antagonist (Liu, *et al.*, 2012). Further, a meta-analysis of 23 studies with close to 5000 subjects showed that depression is associated with increased levels of oxidative stress markers (Palta, *et al.*, 2014). As statins have both anti-inflammatory and antioxidant properties, these could be the main mechanisms of action for their effectiveness in improving depression. While all statins are effective in reducing cholesterol levels, there are

some differences in chemical properties between statins and these may have a potential impact on their efficacy in treating depression. For instance, some statins are more lipophilic than others and these differences affect their ability to cross blood-brain barrier. Lovastatin and simvastatin cross the blood brain barrier more easily in comparison to pravastatin and atorvastatin. A head to head statin comparison trial of atorvastatin and simvastatin on decreasing depressive symptoms showed that in those who were allocated to the simvastatin group showed greater improvements in Hamilton Depression rating scale scores in comparison to the atorvastatin group (Abbasi *et al.*, 2015). Further, the simvastatin group had a faster response to treatment showing improvements earlier than the atorvastatin group (Abbasi *et al.*, 2015). If it is true that the reasons statins have an effect on depressed people is due to inflammation found in the brain it could mean that using a statin which can easily cross the BBB and work directly on the brain has a more powerful antidepressant effect.

It has also been suggested that the efficacy of statins in improving depressive symptoms might be secondary to improvements in quality of life observed in those taking statins which result in decreased incidence of cardiovascular events (Yang, *et al.*, 2003). Depression is a significant risk factor in those with cardiovascular disease. By decreasing the chances of developing a cardiovascular disease with statin treatment, the patient's quality of life can improve and symptoms of depression can be reduced. It can be assumed that those who have cardiovascular diseases are likely to be less healthy, and are more susceptible to developing depression due to these health issues and other comorbidities. Therefore, using a statin to treat and or prevent cardiovascular events from reoccurring can lead to an increased quality of life and decreased likelihood of developing depression. Usually the lipid lowering effect produced by statins is immediate, however it can take a few years of use to provide a decreased risk of cardiovascular

incidences to be seen. Those who take prolonged statin therapy are more likely to be more health conscious leading to better adherence to medications.

Another possibility is that inflammation and oxidative stress predispose individuals to both cardiovascular disease (Arévalo-Lorido, 2016) and depression. Therefore, statins by reducing inflammation and oxidative stress may help reduce the likelihood of cardiovascular events and depression. Lastly, it has also been suggested that statins improve brain perfusion and oxygenation (Glueck, *et al.*, 1993) and thus improve depression. Whatever the mechanism might be, the results of the current meta-analysis provide optimism for further investigating the efficacy of statins in larger trials to confirm these findings.

Limitations

This systematic review and meta-analyses has some limitations. Many studies included in this meta-analysis were allocated an unknown risk of bias based on the Cochrane tool. This determination was usually due to a lack of explanation of key study design issues in methods in several studies. The trials utilized different rating scales and questionnaires to assess the outcome measure of interest (i.e. depressive symptoms experienced by the participants). Some used the Hamilton Depression rating scale, while others used the CES-D. One paper even used a variation of a General Health questionnaire. Due to the variations in scales, it is hard to compare them to each other as they are all scored in different ways. Some of the scales used were self-administered and some were administered by a health care professional. This can cause variations in results obtained. With a self-administered scale, a participant could have for example misinterpreted a question, on the other hand with a scale administered by a health care professional, the participant could have felt pressured to answer the question in a certain way.

The comprehensive meta-analysis software used did not take into account the risk of bias of each study. In this regard, the Cochrane collaborators RevMan-5 software might have been better as that program takes into account the risk of bias as well as the sample size and weights for each study in the analysis accordingly. However, to address heterogeneity, a random effects model was used in this meta-analysis which is a more conservative means to estimate the standardized mean difference between the groups.

Conclusion

The findings of this systematic review provide preliminary evidence that statins are an effective adjunctive treatment in those who are clinically depressed. In those who are not depressed, the use of statins does not appear to be associated with any significant benefit in improving depression. This, however, may be because these patients have limited depressive symptoms and thus not much room for improvement. Importantly, the evidence suggests that statin use in such populations is not associated with induction or worsening of depressive symptoms. Therefore, the current meta-analysis clearly refutes the findings of some trials which stated that statins induce depressive symptoms in non-depressed populations. While the results of the current meta-analysis are very promising and supportive of benefits of statin therapy, further research and trials with larger sample sizes need to be conducted in order to fully explore the benefits of statins in depressed and non-depressed populations.

Author Statement

Contributors

Megha Yatham conducted the database searches and the papers identified were independently reviewed by both Megha Yatham and Kavya yatham for inclusion. Any disputes or conflicts related to selection of papers were resolved in consultation with Arun Ravindran. The data analysis was conducted by Megha Yatham and Kavya Yatham and the manuscript was written by Megha Yatham with the guidance from Frank Sullivan. The prepared manuscript was critically reviewed and edited by all the authors.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of Interest Disclosures

Megha Yatham, Kavya Yatham and Frank Sullivan declare no conflicts. Arun Ravindran has received grant and research support from AstraZeneca, Bristol-Myers Squibb, Cephalon, Eli Lilly, GlaxoSmithKline, Janssen-Ortho, Lundbeck, Pfizer, Roche, Servier and Wyeth. Current industry grant awards: Janssen-Ortho. Dr Ravindran has also served as a consultant for some of the above institutions and on their Advisory Boards. He has also participated in CME programs sponsored by these and other pharmaceutical companies, such as Sunovion. He also holds or have held peer-reviewed funding from Canadian Institutes of Health Research, Grand Challenges Canada, Ontario Brain Institute, Ontario Mental Health

Foundation, Canadian Foundation for Innovation and Ministry of Economic Development and Innovation, and National Institutes of Mental Health

Acknowledgements

None

ACCEPTED MANUSCRIPT

References

- Abbasi, S.H., Mohammadinejad, P., Shahmansouri, N., Salehiomran, A., Beglar, A.A., Zeinoddini, A., Forghani, S., Akhondzadeh, S., 2015. Simvastatin versus atorvastatin for improving mild to moderate depression in post-coronary artery bypass graft patients: A double-blind, placebo-controlled, randomized trial. *Journal of Affective Disorders* 183, 149–155. doi:10.1016/j.jad.2015.04.049
- American Psychiatric Association 2013. *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5)*, Diagnostic and Statistical Manual of Mental Disorders 5th edition, 280. doi: 10.1176/appi.books.9780890425596.744053.
- Arévalo-Lorido, J.C., 2016. Clinical relevance for lowering C-reactive protein with statins. *Annals of Medicine* 48, 516–524. doi:10.1080/07853890.2016.1197413
- Beck, A.T., Ward, C.H., Mendelson, M., Mock, J., Erbaugh, j., 1961. An inventory for measuring depression. *Arch Gen Psychiatry*.4, 561-571
- Benros, M.E., Waltoft, B.L., Nordentoft, M., Østergaard, S.D., Eaton, W.W., Krogh, J., Mortensen, P.B., 2013. Autoimmune Diseases and Severe Infections as Risk Factors for Mood Disorders. *JAMA Psychiatry* 70, 812. doi:10.1001/jamapsychiatry.2013.1111

Chan, D., Binks, S., Nicholas, J. M., Frost, C., Cardoso, M. J., Ourselin, S., Wilkie, D., Nicholas, R., Chataway, J., 2017. Effect of high-dose simvastatin on cognitive, neuropsychiatric, and health-related quality-of-life measures in secondary progressive multiple sclerosis: secondary analyses from the MS-STAT randomised, placebo-controlled trial. *The Lancet. Neurology*, 16(8), 591-600. doi: [https://dx.doi.org/10.1016/S1474-4422\(17\)30113-8](https://dx.doi.org/10.1016/S1474-4422(17)30113-8)

Devaraj, S., Rogers, J. and Jialal, I., 2007 Statins and biomarkers of inflammation. *Current Atherosclerosis Reports*, 33–41. doi: 10.1007/BF02693938.

Gengo, F. , Cwudzinski, D. , Kinkel, P. , Block, G. , Stauffer, L. and Lines, C., 1995. Effects of treatment with lovastatin and pravastatin on daytime cognitive performance. *Clin Cardiol*, 18, 209-214. doi:10.1002/clc.4960180406

Ghanizadeh, A. and Hedayati, A., 2013. Augmentation of fluoxetine with lovastatin for treating major depressive disorder, a randomized double-blind placebo controlled-clinical trial. *Depression and anxiety*. 30(11), 1084–1088. doi: <https://dx.doi.org/10.1002/da.22195>.

Glueck, C.J., Tieger, M., Kunkel, R., Tracy, T., Speirs, J., Streicher, P., Illig, E., 1993. Improvement in symptoms of depression and in an index of life stressors accompany treatment of severe hypertriglyceridemia. *Biological Psychiatry* 34, 240–252. doi:10.1016/0006-3223(93)90078-r

- Gougol, A., Zareh-Mohammadi, N., Raheb, S., Farokhnia, M., Salimi, S., Iranpour, N., Akhondzadeh, S., 2015. Simvastatin as an adjuvant therapy to fluoxetine in patients with moderate to severe major depression: A double-blind placebo-controlled trial. *Journal of Psychopharmacology* 29(5), 575–581. <https://dx.doi.org/10.1177/0269881115578160>.
- Haghighi, M., Khodakarami, S., Jahangard, L., Ahmadpanah, M., Bajoghli, H., Holsboer-Trachsler, E., Brand, S., 2014. In a randomized, double-blind clinical trial, adjuvant atorvastatin improved symptoms of depression and blood lipid values in patients suffering from severe major depressive disorder. *Journal of Psychiatric Research* 58, 109–114.
doi:10.1016/j.jpsychires.2014.07.018
- Hamilton, M., 1960. A rating scale for depression. *Journal of Neurology, Neurosurgery & Psychiatry* 23, 56–62. doi: 10.1136/jnnp.23.1.56.
- Harrison, R. W. and Ashton, C. H., 1994. Do cholesterol-lowering agents affect brain activity? A comparison of simvastatin, pravastatin, and placebo in healthy volunteers. *British journal of clinical pharmacology* 37(3), 231–236.
- Hasin, D.S., Sarvet, A.L., Meyers, J.L., Saha, T.D., Ruan, W.J., Stohl, M., Grant, B.F., 2018. Epidemiology of Adult DSM-5 Major Depressive Disorder and Its Specifiers in the United States. *JAMA Psychiatry* 75, 336. doi:10.1001/jamapsychiatry.2017.4602

Higgins, J.P., Altman, D.G., Gotzsche, P.C., Jüni, P., Moher, D., Oxman, A.D., Savovic, J., Schulz, K.F., Weeks, L., Sterne, J.A.; Cochrane Bias Methods Group.; Cochrane Statistical Methods Group.,2011. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*, 343: d5928.

doi: 10.1136/bmj.d5928

Husain, M. I., Strawbridge, R., Stokes, P.R., Young, A.H., 2017. Anti-inflammatory treatments for mood disorders: Systematic review and meta-analysis', *Journal of Psychopharmacology*, 31(9), pp. 1137–1148. doi: 10.1177/0269881117725711.

Hyypä, M.T., Kronholm, E., Virtanen, A., Leino, A., Jula, A., 2003. Does simvastatin affect mood and steroid hormone levels in hypercholesterolemic men? A randomized double-blind trial. *Psychoneuroendocrinology* 28, 181–194. doi:10.1016/s0306-4530(02)00014-8

Kim, S. W., Bae, K. Y., Kim, J. M., Shin, I. S., Hong, Y. J., Ahn, Y., Jeong, M. H., Berk, M., Yoon, J. S., 2015. The use of statins for the treatment of depression in patients with acute coronary syndrome. *Translational psychiatry* 5(8), e620. doi:10.1038/tp.2015.116

Köhler, O., Gasse, C., Petersen, L., Ingstrup, K.G., Nierenberg, A.A., Mors, O., Østergaard, S.D., 2016. The Effect of Concomitant Treatment With SSRIs and Statins: A Population-Based Study. *American Journal of Psychiatry* 173, 807–815. doi:10.1176/appi.ajp.2016.15040463

Liu, Y., Ho, R. C. M. and Mak, A., 2012. Interleukin (IL)-6, tumour necrosis factor alpha (TNF- α) and soluble interleukin-2 receptors (sIL-2R) are elevated in patients with major depressive disorder: A meta-analysis and meta-regression. *Journal of Affective Disorders* 139(3), 230–239. doi: 10.1016/j.jad.2011.08.003.

Morales, K., Wittink, M., Datto, C., Difilippo, S., Cary, M., Tenhave, T., Katz, I.R., 2006. Simvastatin Causes Changes in Affective Processes in Elderly Volunteers. *Journal of the American Geriatrics Society* 54, 70–76. doi:10.1111/j.1532-5415.2005.00542.x

Muldoon, M.F., Barger, S.D., Ryan, C.M., Flory, J.D., Lehoczky, J.P., Matthews, K.A., Manuck, S.B., 2000. Effects of lovastatin on cognitive function and psychological well-being. *The American journal of medicine*, 108(7), 538–546.

O'neil, A., Sanna, L., Redlich, C., Sanderson, K., Jacka, F., Williams, L.J., Pasco, J.A., Berk, M., 2012. The impact of statins on psychological wellbeing: a systematic review and meta-analysis. *BMC Medicine* 10. doi:10.1186/1741-7015-10-154

Ormiston, T., Wolkowitz, O.M., Reus, V.I., Manfredi, F., 2003. Behavioral Implications of Lowering Cholesterol Levels: A Double-Blind Pilot Study. *Psychosomatics* 44, 412–414. doi:10.1176/appi.psy.44.5.412

Palta, P., Samuel, L.J., Miller, E.R., Szanton, S.L., 2014. Depression and Oxidative Stress. *Psychosomatic Medicine* 76, 12–19. doi:10.1097/psy.0000000000000009

Parsaik, A.K., Singh, B., Hassan, M.M., Singh, K., Mascarenhas, S.S., Williams, M.D., Lapid, M.I., Richardson, J.W., West, C.P., Rummans, T.A., 2014. Statins use and risk of depression: A systematic review and meta-analysis. *Journal of Affective Disorders* 160, 62-67
<https://doi.org/10.1016/j.jad.2013.11.026>.

Qatar Computing Research Institute (Data Analytics), 2016. Rayyan — a web and mobile app for systematic reviews. Available at: <https://rayyan.qcri.org/welcome> (Accessed: February 9, 2018).

Redlich, C., Berk, M., Williams, L.J., Sundquist, J., Sundquist, K., Li, X., 2014. Statin use and risk of depression: a Swedish national cohort study. *BMC Psychiatry* 14. doi:10.1186/s12888-014-0348-y

Robertson, C.S., McCarthy, J.J., Miller, E.R., Levin, H., Mccauley, S.R., Swank, P.R., For The Mission Connect Mild Tbi Tr, 2017. Phase II Clinical Trial of Atorvastatin in Mild Traumatic Brain Injury. *Journal of Neurotrauma* 34, 1394–1401. doi:10.1089/neu.2016.4717

Rush, A.J., Trivedi, M.H., Wisniewski, S.R., Nierenberg, A.A., Stewart, J.W., Warden, D., Niederehe, G., Thase, M.E., Lavori, P.W., Lebowitz, B.D., McGrath, P.J., Rosenbaum, J.F., Sackeim, H.A., Kupfer, D.J., Luther, J., Fava, M., 2006. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry*. 163:1905–1917

Salagre, E., Fernandes, B.S., Dodd, S., Brownstein, D.J., Berk, M., 2016. Statins for the treatment of depression: A meta-analysis of randomized, double-blind, placebo-controlled trials. *Journal of Affective Disorders* 200, 235-242. <https://doi.org/10.1016/j.jad.2016.04.047>.

Sarkar, S. and Schaefer, M., 2014. Antidepressant pretreatment for the prevention of interferon alfa-associated depression: A systematic review and meta-analysis. *Psychosomatics* 55(3), 221–234. doi: 10.1016/j.psych.2013.06.015.

Sparks, D.L., Sabbagh, M.N., Connor, D.J., Lopez, J., Launer, L.J., Browne, P., Wasser, D., Johnson-Traver, S., Lochhead, J., Ziolkowski, C., 2005. Atorvastatin for the Treatment of Mild to Moderate Alzheimer Disease. *Archives of Neurology* 62, 753. doi:10.1001/archneur.62.5.753

Stewart R.A., Sharples K.J., North F.M., Menkes, D.B., Baker, J., Simes, J., 2000. Long-term Assessment of Psychological Well-being in a Randomized Placebo-Controlled Trial of Cholesterol Reduction With Pravastatin. *Arch Intern Med* 160(20), 3144–3152. doi:10.1001/archinte.160.20.3144

University of Alberta Libraries, 2018. Systematic Reviews -Searching the Literature-search filters. Available at: <https://guides.library.ualberta.ca/c.php?g=248586&p=1655962> (Accessed: 5th February 2018).

University of Texas, 2017. Search Filters for Various Databases: Ovid PsycINFO. Available at: http://libguides.sph.uth.tmc.edu/search_filters/ovid_psycinfo_filters (Accessed: 8th February 2018).

Wardle, J., Armitage, J., Collins, R., Wallendszus, K., Keech, A., Lawson, A., 1996. Randomised placebo controlled trial of effect on mood of lowering cholesterol concentration. *Bmj* 313, 75–78. doi:10.1136/bmj.313.7049.75

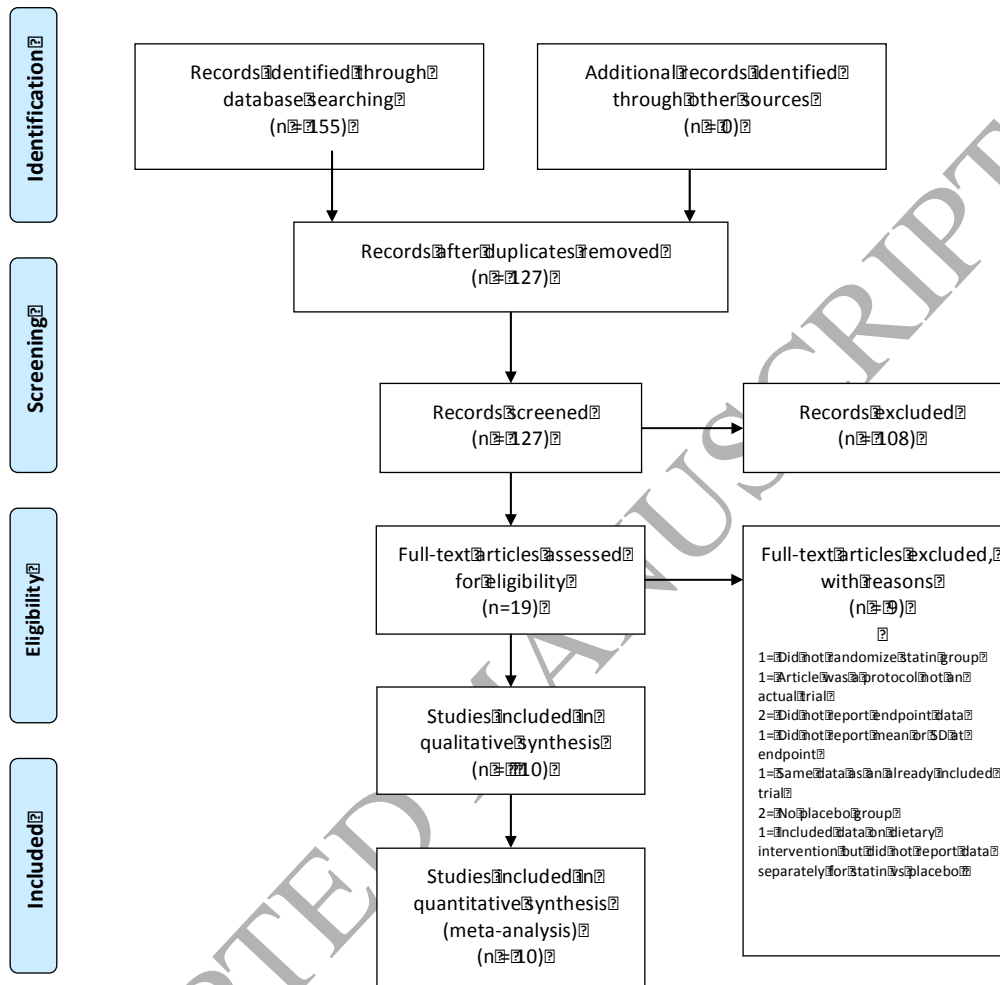
WHO Collaborating Centre for Drug Statistics Methodology, 2017. DDD index HMG CoA reductase inhibitors. Available at: https://www.whocc.no/atc_ddd_index/?code=C10AA&showdescription=yes (Accessed: 9th April 2018).

WHO | Depression, 2017. WHO. World Health Organization. Available at: <http://www.who.int/mediacentre/factsheets/fs369/en/> (Accessed: 20 February 2018).

Yang, C.-C., Jick, S. S. and Jick, H., 2003. Lipid-Lowering Drugs and the Risk of Depression and Suicidal Behavior. *Archives of Internal Medicine* 163(16), 1926. doi: 10.1001/archinte.163.16.1926.

Yesavage, J.A., Brink, T.L., Rose, T.L., Lum, O., Huang, V., Adey, M., Leirer, V.O..1982. Development and validation of a geriatric depression screening scale: a preliminary report. *J Psychiatr Res.*1983;17(1):37-4

Figure 1



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

Figure 2: Effects of Statins on Depressive Symptoms

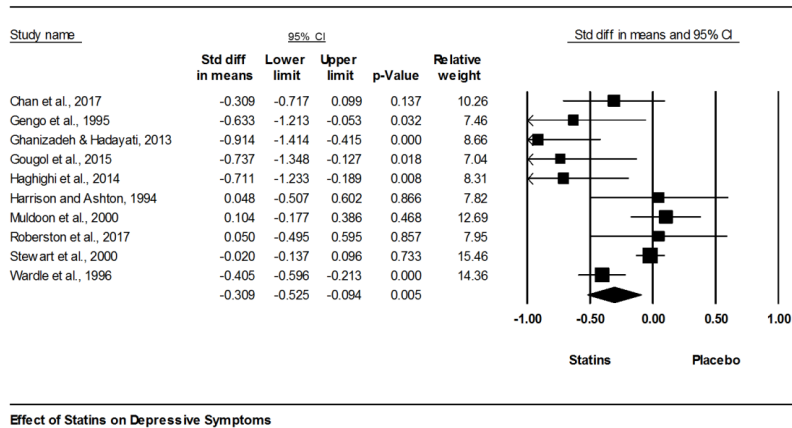


Figure 3: Effects of Statins on Depressive Symptoms in Depressed and Non-Depressed Populations

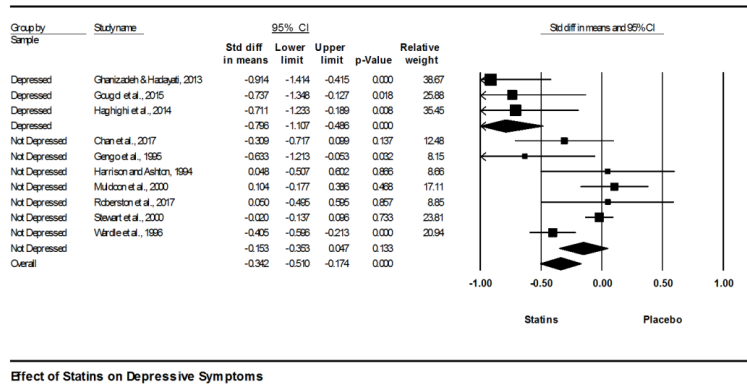


Table 1: A summary of Studies included

	Study population	Study design	Follow up date(s)	Depression rating scale used
Chan et al., 2017	Patients aged 18-65 years meeting McDonald diagnostic criteria for Multiple sclerosis	Double blind, parallel group randomised placebo controlled trial	6, 12, 18, and 24 months	Hamilton Depression Rating Scale
Gengo et al., 1995	Patients aged 40-60 years with primary moderate hypercholesterolemia	Double blind placebo controlled two period incomplete block crossover study	Day 29	Profile of mood states: the monopolar form of this commercially available test was used.
Ghanizadeh and Hadayati, 2013	Patients diagnosed with MDD per Diagnostic and Statistical Manual of Mental Disorders (fourth edition)	Randomized double blind placebo controlled trial	Week 6	Hamilton Depression Rating Scale
Gougal et al., 2015	Patients aged 20-70 who have a MDD based upon Diagnostic and Statistical Manual of Mental Disorders (fourth edition), with a HDRS of 22 or higher	Parallel-group, double blind, placebo controlled clinical trial	Week 6	Hamilton Depression Rating Scale
Haghighi et al., 2014	Patients with a current unipolar depressive disorder per the Diagnostic and Statistical Manual of Mental Disorder, Hamilton depression rating score of 25 or higher.	Randomized double blind placebo controlled trial	Week 12	Hamilton Depression Rating Scale
Harrison and Ashton, 1994	Healthy patients aged 20-32	Double-blind, placebo-controlled, randomised crossover study	Week 4	Hospital Anxiety and Depression Rating Scale
Muldoon et al., 2000	Generally healthy patients aged 24-60 years with hypercholesterolemia	Randomized double blind placebo controlled trial	6 Months	Hamilton Depression Rating Scale
Robertson et al., 2017	Patients aged 18-50 with injury occurring with the preceding 24 our and no hospitalization for the injury for which the participant enrolled.	Randomized placebo controlled trial	Day 7, 1 and 3 months	The Centre for Epidemiologic Studies-Depression scale (CES-D)
Stewart et al., 2000	Patients aged 31-74 years with fasting serum cholesterol level of 4.0-7.0 mmol/L, and have a history of acute myocardial infarction, or hospitalization for unstable angina in the previous 3-36 months	Randomized double placebo trial	6 months, 1,2,3 and 4 Years	30- question version of the General Health Questionnaire (GHQ)
Wardle et al., 1996	Patients aged 40-75 years with blood total cholesterol concentration of 3.5mmol/l or greater and are considered to be at a higher risk of coronary heart disease, angina pectoris, stroke, transient ischemic attack, peripheral vascular disease, treated diabetes mellitus, or hypertension)	Randomized placebo controlled trial	Week 152	Shortened version of the profile of mood state questionnaire

	Intervention	Treatment	Patients allocated to each treatment	Mean score at endpoint
Chan et al., 2017	Simvastatin 80 mg or	Simvastatin	50	11.04 (6.13)
	Placebo once daily	Placebo	44	13.02 (6.71)
Gengo et al., 1995	Lovastatin 40mg or	Lovastatin	24	2.1 (2.4)
	Placebo taken with the evening meal	Placebo	24	4.0 (3.5)
Ghanizadeh and Hadayati, 2013	Lovastatin 30mg or	Lovastatin	34	16.3 (3.16)
	Placebo once daily with fluoxetine up to 40mg per day	Placebo	34	20.4 (5.5)
Gougol et al., 2015	Simvastatin 20mg or	Simvastatin	22	6.5 (7.1)
	Placebo once daily with Fluoxetine 20mg once daily for the first 2 weeks then 40mg once daily	Placebo	22	11.31 (5.89)
Haghigil et al., 2014	Atorvastatin 20mg or	Atorvastatin	30	19.63 (3.16)
	Placebo once daily	Placebo	30	22.03 (3.58)
Harrison and Ashton, 1994	Simvastatin 40mg or	Simvastatin	25	1.6 (2.2)
	Placebo once daily	Placebo	25	1.5 (2)
Muldoon et al., 2000	Lovastatin 20mg or	Lovastatin	98	3.1 (4.3)
	Placebo once daily	Placebo	96	2.7 (3.3)
Robertson et al., 2017	Atorvastatin 1mg/kg (up to 80 mg) or	Atorvastatin	28	6 (12.3)
	Placebo once daily	Placebo	24	5.5 (6.3)
Stewart et al., 2000	Pravastatin sodium 40mg or Placebo once daily	Pravastatin Sodium	559	22.6 (10.1)
		Placebo	571	22.8 (9.6)
Wardle et al., 1996	Simvastatin 20mg or	Simvastatin	334	8 (3.8)
	Placebo once daily	Placebo	157	9.5 (3.5)