



Review article

The effects of statin monotherapy on depressive symptoms: A systematic review and meta-analysis

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ABSTRACT

Introduction: Statins have been proposed as a strategy for treating depression, but their benefit in the absence of concurrent antidepressant treatment is unclear. This meta-analysis investigated the antidepressant effects of statin monotherapy in the general population.

Methods: We conducted a literature search of randomised controlled trials using any statin monotherapy versus any control condition for depressive symptoms. Our primary efficacy outcome was the mean value on any standardised scale for depression at study endpoint. We also measured efficacy at three further timepoints (<6 months, 6–12 months, >12 months), as well as acceptability, tolerability, and safety. Respectively, continuous and dichotomous outcomes were computed using standardised mean difference (SMD) or relative risk (RR) with 95% confidence intervals (CI) using a random-effect model.

Results: Pooled analyses did not show that statin monotherapy improves depressive symptoms at endpoint ($N = 2712$ SMD = -0.18 ; 95% CI = -0.41 to 0.04), nor at any other specific timepoint. No difference between statins and control was identified for any of the other outcome measures.

Discussion: These results differ from those of previous meta-analyses and, compounded by more recently available evidence, suggest that statins may not have intrinsic antidepressant properties, but may be useful for the management of depression in add-on to antidepressants.

Limitations: Data from heterogeneous populations and using different statins were pooled, though several sensitivity and subgroup analyses were performed to account for that.

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https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=306653

1. Introduction

Statins (3-hydroxy-3-methylglutaryl-Coenzyme A reductase inhibitors) are a class of anti-cholesterolemic drugs licensed for the prevention and treatment of cardiovascular and metabolic disorders and their complications (Health NCCfM, 2020). Besides their lipid-lowering properties, statins have widespread activity on neurobiological, cardiometabolic, and immunological systems that have been implicated in the pathophysiology of mood disorders, especially depression (Walker et al., 2021). While there are hints that statins may benefit depression in some specific subgroups, for example in patients with comorbid cardiovascular illness (Kim et al., 2019) or in the circumstances described

below, it is uncertain whether statin use is associated with a generalised positive effect on depressive symptoms.

A meta-analysis of randomised controlled trials in patients diagnosed with depressive disorder showed that statins in addition to antidepressants are more efficacious than antidepressants plus placebo in reducing depressive symptoms after at least two months of treatment [$N = 238$; standardised mean difference (SMD) = -0.48 ; 95% confidence interval (CI) = -0.74 to -0.22] (De Giorgi et al., 2021a). A real-world cohort study we have recently conducted on a similar, larger population indicates that statin use is associated with fewer discontinuations of antidepressants due to any cause [$N = 673,177$; odds ratio (OR) = 0.88 ; 99% CI = 0.85 to 0.91] and adverse events ($N = 673,177$; OR = 0.92 ;

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99% CI = 0.87 to 0.98) (unpublished data). Overall, evidence suggests that statin add-on to antidepressants may be a promising and viable strategy for the treatment of people with depression.

Whether statins can reduce depressive symptoms regardless of concurrent use of antidepressant medications is a more equivocal matter (Köhler-Forsberg et al., 2020). A previous meta-analysis of trials investigating statins with and without antidepressants in mixed populations with subclinical and clinical depression described overall benefits of statins on depression rating scores ($N = 2517$; $SMD = -0.31$; 95% CI = -0.52 to -0.09), but this outcome appeared mostly driven by those few studies that had employed statins along with antidepressants in patients diagnosed with depression (Yatham et al., 2019). A similar issue (De Giorgi et al., 2021b) may have affected a previous network meta-analysis that aimed to assess the comparative efficacy of different statins and had indicated an overall positive effect of statins compared to placebo ($SMD = -0.35$; 95% CI -0.59 to -0.11), with atorvastatin ranking higher in terms of antidepressant efficacy (mean difference = -3.46 ; 95% CI -5.26 to -1.67) (Lee et al., 2021a). Findings from observational studies seem more conflicting, since both no effect ($N = 5,035,070$; OR = 0.87; 95% CI = 0.74 to 1.02) (Lee et al., 2021b) and a reduction [$N = 1,149,384$; hazard ratio (HR) = 0.91; 95% CI = 0.88 to 0.94] (Molero et al., 2020) in incident depression were found for statin-users. Mechanistic studies in vitro and in animals (De Giorgi et al., 2021c) as well as experimental medicine trials in healthy volunteers (De Giorgi et al., 2021d; De Giorgi et al., 2022) have similarly reported ambiguous results.

In view of this uncertainty, we conducted a systematic review and meta-analysis of randomised controlled trials to investigate the effect on depressive symptoms of any statin monotherapy in adult participants with subclinical depression.

2. Methods

The protocol for this review was registered on PROSPERO international prospective register of systematic reviews with reference CRD42022306653 and is available at https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=306653.

2.1. Search strategy

We run an extensive search of the MEDLINE, Embase, and PsycINFO databases via Ovid SP, as well as Cochrane CENTRAL, ClinicalTrials.gov, and WHO portal, from the date of inception until the 22nd of January 2022, with no language restrictions. We also performed a manual screening of the references of the included articles to identify additional relevant trials. The search algorithms combined index terms and free-text words for statins, depression/depressive symptoms, and clinical trials (Supplementary Material, S1).

2.2. Inclusion criteria

We only included randomised controlled trials that compared the effects of any statin monotherapy (i.e., not in add-on to any antidepressant strategy) versus any control condition on depressive symptoms. For cross-over trials, we extracted and analysed data from the first randomisation period when possible. Studies involving adults (i.e., aged 18 years or older) of both sexes were included irrespective of patients' diagnoses for physical or mental health disorders.

2.3. Outcomes

For efficacy, measured as change in depression score, we calculated results at studies' endpoints as well as at the following timepoints (or their closest in a contiguous range): early (<6 months), medium (6–12 months), long (>12 months). For acceptability, tolerability, and safety we calculated results at the studies' endpoints.

2.4. Primary outcome

The primary efficacy outcome measure was the mean value on any standardised scale for depressive symptoms (e.g., Center for Epidemiologic Studies Depression Scale, Geriatric Depression Scale, Hamilton Depression Rating Scale) at studies' endpoint.

2.5. Secondary outcomes

Secondary outcomes included:

- Efficacy, measured as the mean value on any standardised scale for depressive symptoms at three timepoints: early (<6 months), medium (6–12 months), long (>12 months).
- Acceptability, measured as the number of participants discontinuing treatment (dropouts) due to any cause at the studies' endpoints.
- Tolerability, measured as the number of participants discontinuing treatment (dropouts) due to adverse events at the studies' endpoints.
- Safety, measured as the number of participants with any adverse events, self-harm episodes, and suicides at the studies' endpoints.

2.6. Study selection, data extraction, quality assessment

Two researchers (NRP, SW) independently screened the retrieved records' title/abstract and assessed the relevant full-text articles for eligibility. Any disagreement was discussed with a third researcher (RDG) and resolved by consensus.

Three researchers (NRP, RDG, SW) used a structured data extraction spreadsheet to ensure consistency of appraisal for each study. For the included studies, data about first authors' name, year of publication, study design, sample size and characteristics, intervention and comparison details, length of follow-up, primary and secondary outcome measures of interest with point estimates were extracted. Graph data was extracted using WebPlotDigitizer v4.2 software (Rohatgi, 2021). For means and standard deviations not readily available, we estimated values from medians and interquartile ranges or the RevMan v5.4 software calculator according to guidelines (JPT et al., 2021; Wan et al., 2014).

We assessed the risk of bias of the included trials using the “RoB 2: A revised Cochrane risk-of-bias tool for randomized trials” (Sterne et al., 2019), and the certainty of evidence for all outcomes via GRADEpro GDT (GRADEpro GDT, 2021). The quality assessment was performed by two independent raters (NRP, RDG) and disagreements were discussed with another member of the review group (SW) and resolved by consensus.

2.7. Statistical analysis

All the extracted data was analysed using STATA v17 software (StataCorp, 2021). Data from rating scales for depression were analysed as a continuous variable using standardised mean difference (SMD, as different rating scales were used) with 95% confidence intervals (CI), employing a random-effect model, more conservative than a fixed-effects model, in view of the heterogeneous study populations included. For evaluating the clinical significance of SMD values, the effect size was considered ‘small’ if $SMD < 0.40$, ‘moderate’ if $SMD = 0.40$ to 0.70 , and ‘large’ if $SMD > 0.70$ (JPT et al., 2021). All the other quantitative data (e.g., number of participants discontinuing treatment) were analysed as dichotomous variables using relative risk (RR) with 95% CI, using random-effect models. For dropouts and adverse events, zero events of both arms in any trial were replaced by 0.5 (JPT et al., 2021), which is recommended when treatment effects are expected to be unlikely on a specific outcome (Cheng et al., 2016). Heterogeneity between studies was investigated through the I^2 , t^2 , and p -value statistic and by visual inspection of the forest plots. Funnel plots and Egger's test were used to detect publication bias. Sensitivity and subgroup analyses

were conducted, as appropriate, to verify the robustness of the primary outcome findings.

3. Results

3.1. Literature search

The literature search was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline (Page et al., 2021) in Fig. 1.

In summary, it retrieved 1385 records from electronic databases (Cochrane CENTRAL: 309; Embase: 961; PubMed/MEDLINE: 87; PsycINFO: ClinicalTrials.gov: 13; WHO portal: 11), and no further papers from the manual search. After duplicates removal, 1132 records' title and abstract were screened by applying the inclusion/exclusion criteria previously described. Fifty-nine potentially eligible articles were assessed full-text, of which 14 were finally included in this systematic review.

3.2. Trials characteristics and risk of bias assessment

The characteristics of the 14 retrieved trials (Carlsson et al., 2002; Chan et al., 2017; Gengo et al., 1995; Harrison and Ashton, 1994; Hyypä et al., 2003; Morales et al., 2006; Muldoon et al., 2000; Robertson et al., 2017; Santanello et al., 1997; Sheridan et al., 2014; Sparks et al., 2005; Stewart et al., 2000; Visseren et al., 2001; Wardle et al., 1996) were reported in Table 1.

The study samples included: nine trials in people with hyperlipidaemia (Carlsson et al., 2002; Gengo et al., 1995; Hyypä et al.,

2003; Morales et al., 2006; Muldoon et al., 2000; Santanello et al., 1997) of which two involving patients with comorbid coronary artery disease (Stewart et al., 2000; Wardle et al., 1996) while one trial included comorbid type-2 diabetes mellitus (Visseren et al., 2001); one trial in healthy volunteers (Harrison and Ashton, 1994); one trial on patients with secondary progressive multiple sclerosis (Chan et al., 2017); one trial in adults with traumatic brain injury (Robertson et al., 2017); one trial in patients diagnosed with mild-to-moderate Alzheimer disease (Sparks et al., 2005); one trial in individuals affected by chronic hepatitis C (Sheridan et al., 2014). All trials had been conducted in an adult population, though three focussed on an older adults group (Carlsson et al., 2002; Morales et al., 2006; Santanello et al., 1997) and one was in males only (Hyypä et al., 2003). Baseline diagnosis of depression and antidepressant use were not always reported (Supplementary Material, S2), but overall rates of both seemed low or were explicitly excluded. The majority of trials employed a lipophilic statin (i.e., simvastatin, lovastatin, atorvastatin, fluvastatin) (Chan et al., 2017; Gengo et al., 1995; Harrison and Ashton, 1994; Hyypä et al., 2003; Morales et al., 2006; Muldoon et al., 2000; Robertson et al., 2017; Santanello et al., 1997; Sheridan et al., 2014; Sparks et al., 2005; Visseren et al., 2001; Wardle et al., 1996), though some used a hydrophilic statin (i.e., pravastatin) (Carlsson et al., 2002; Gengo et al., 1995; Harrison and Ashton, 1994; Stewart et al., 2000). The range of follow-up was very wide between 4 and 152 weeks.

The risk of bias tables, including explanatory notes and overall bias across trials are reported in Supplementary Material, S2. In summary, we judged nine trials to be at 'low' risk of bias (Chan et al., 2017; Gengo et al., 1995; Harrison and Ashton, 1994; Hyypä et al., 2003; Muldoon et al., 2000; Santanello et al., 1997; Sheridan et al., 2014; Sparks et al.,

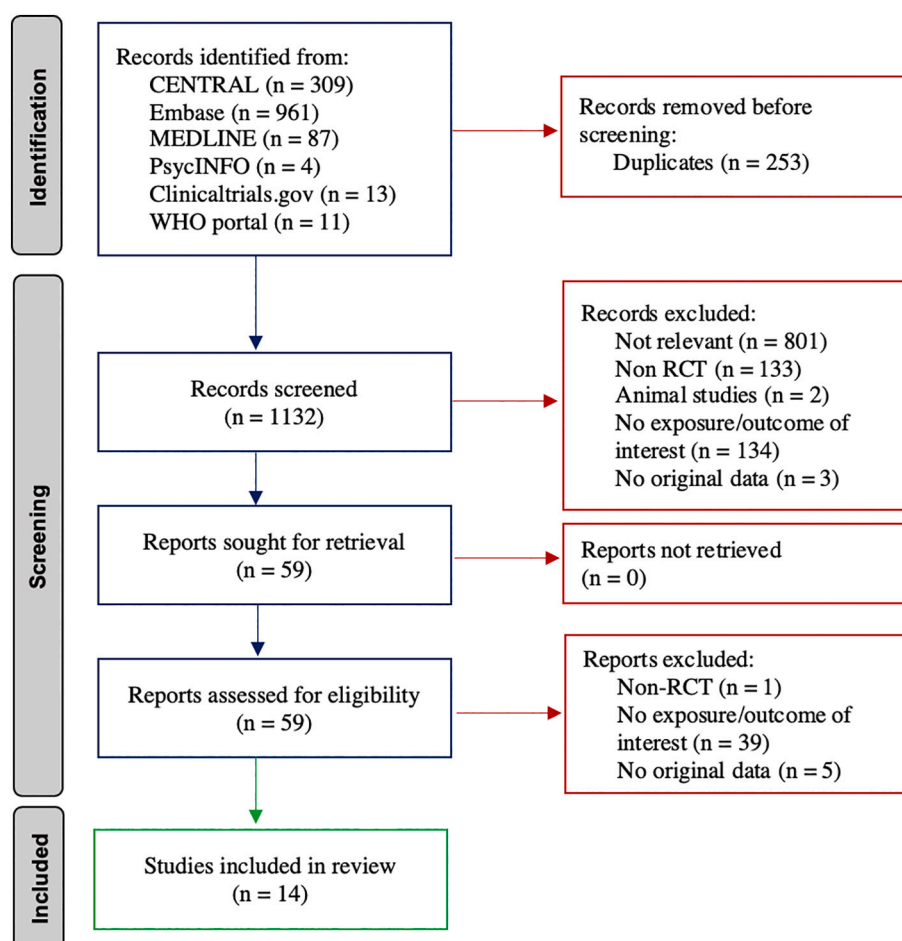


Fig. 1. PRISMA 2020 flow diagram.

Table 1
Trials characteristics.

Study ID	Study design	Population	Intervention	Comparator	Follow-up	Primary outcome measure scale
Carlsson 2002	RCT crossover	41 hyperlipidaemic older adults aged ≥ 70 years	Pravastatin 20 mg, then pravastatin 20 mg + tocopherol 400 IU	Placebo + tocopherol, then pravastatin + tocopherol	1 year	GDS
Chan 2017	RCT	140 secondary progressive multiple sclerosis adults	Simvastatin 80 mg	Placebo	2 years	HDRS
Gengo 1995	RCT crossover	36 hyperlipidaemic adults	Lovastatin 40 mg, pravastatin 40 mg	Placebo	4 weeks	POMS
Harrison 1994	RCT crossover	25 healthy adults	Simvastatin 40 mg, pravastatin 40 mg	Placebo	4 weeks	HADS
Hyypä 2003	RCT crossover	120 hyperlipidaemic men aged 35–64 years	Simvastatin 20 mg	Placebo	24 weeks	BDI
Morales 2006	RCT	80 hyperlipidaemic older adults aged ≥ 65 years	Simvastatin (up to) 20 mg	Placebo	15 weeks	CES-D
Muldoon 2000	RCT	209 hyperlipidaemic adults	Lovastatin 20 mg	Placebo	6 months	HDRS
Robertson 2017	RCT	52 mild TBI adults aged 18–50 years	Atorvastatin 1 mg/kg/die (up to 80 mg/die)	Placebo	3 months	CES-D
Santanello 1997	RCT	431 hyperlipidaemic older adults aged ≥ 65 years	Lovastatin 20–40 mg	Placebo	6 months	CES-D
Sheridan 2014	RCT	60 chronic hepatitis C adults	Fluvastatin 40–80 mg, Fluvastatin 40–80 mg + n-3 PUFA 1 g, Fluvastatin 40–80 mg + n-3 PUFA 2–4 g	Placebo, n-3 PUFA 1 g, n-3 PUFA 2–4 g	12 weeks	HADS
Sparks 2005	RCT	63 mild-to-moderate Alzheimer disease adults	Atorvastatin 80 mg	Placebo	12 months	GDS
Stewart 2000	RCT	1130 hyperlipidaemic adults with CAD	Pravastatin 40 mg	Placebo	4 years	GHQ
Visseren 2001	RCT	87 hyperlipidaemic adults with type 2 diabetes mellitus	Fluvastatin 40 mg	Placebo	12 weeks	Zung SDS
Wardle 1996	RCT	621 hyperlipidaemic adults aged 40–75 years with CAD	Simvastatin 20–40 mg	Placebo	3 years	POMS

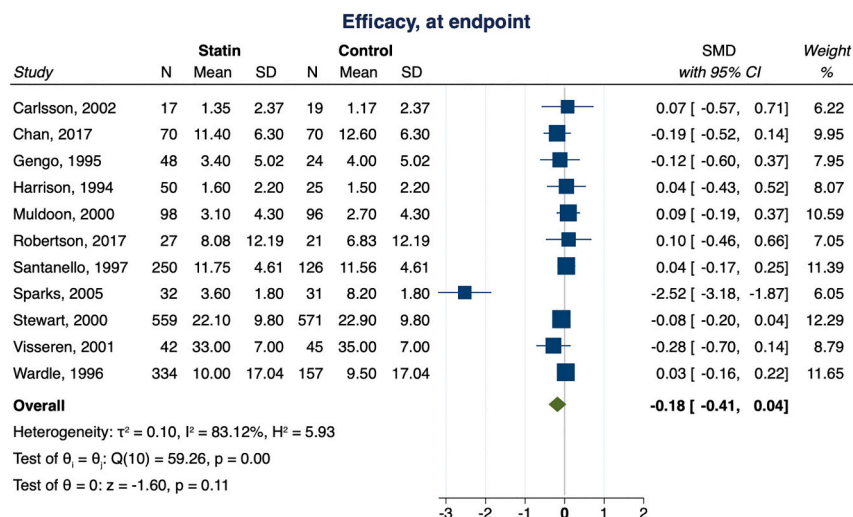
BDI = Beck Depression Inventory; CAD = coronary artery disease; CES-D = Centre for Epidemiological Studies Depression; GDS = Geriatric Depression Scale; GHQ = General Health Questionnaire; HADS = Hospital Anxiety and Depression Scale; HDRS = Hamilton Depression Rating Scale; n-3 PUFA = omega-3 ethyl esters; POMS = Profile of Mood States; RCT = Randomised Controlled Trial; SDS = Self-Rating Depression Scale; TBI = Traumatic Brain Injury.

2005; Stewart et al., 2000) and five with ‘some concerns’ (Carlsson et al., 2002; Morales et al., 2006; Robertson et al., 2017; Visseren et al., 2001; Wardle et al., 1996). All trials described appropriate randomisation procedures, so they scored ‘low’ for this crucial domain. A common reason for downgrading several trials was the lack of an intention-to-treat analysis (Harrison and Ashton, 1994; Hyypä et al., 2003; Morales et al., 2006; Robertson et al., 2017; Visseren et al., 2001; Wardle et al., 1996) despite the presence of missing data. Many trials lacked a pre-specified statistical analysis or pre-registered protocol (Harrison and Ashton, 1994; Hyypä et al., 2003; Morales et al., 2006; Muldoon et al., 2000; Robertson et al., 2017; Santanello et al., 1997; Sparks et al., 2005;

Stewart et al., 2000; Visseren et al., 2001; Wardle et al., 1996), but it should be noted that the latter was not usual practice at the time that the majority of these studies had been conducted.

3.3. Data analysis

For all outcomes, forest plots (below and in the Supplementary Material) display the effect sizes (SMD for continuous outcomes, RR for dichotomous outcomes) with 95% CI from each individual trial, as well as pooled results and heterogeneity. Certainty of the evidence was reported in the GRADE table (see Supplementary Material, S4).

**Fig. 2.** Forest plot for efficacy (mean value for depressive symptoms) at endpoint.

3.4. Efficacy

Eleven trials (Carlsson et al., 2002; Chan et al., 2017; Gengo et al., 1995; Harrison and Ashton, 1994; Muldoon et al., 2000; Robertson et al., 2017; Santanello et al., 1997; Sparks et al., 2005; Stewart et al., 2000; Visseren et al., 2001; Wardle et al., 1996) comprising a total of 2712 participants were included in the meta-analysis for the primary outcome of efficacy as mean value on any standardised scale for depressive symptoms at studies' endpoint (Fig. 2). This showed a small effect of statins in improving depressive scores compared to placebo that did not reach statistical significance (SMD = -0.18 ; 95% CI = -0.41 to 0.04). We scored the degree of certainty for this outcome as 'very low', due to serious concerns about inconsistency, indirectness, and imprecision. No publication bias was identified (Supplementary Material, S5). Heterogeneity was substantial ($I^2 = 83.12\%$) and driven only by one study (Sparks et al., 2005), which had found a large positive effect of statins on depressive scores in a sample of patients with mild-to-moderate Alzheimer's disease (N = 63; SMD = -2.52 ; 95% CI = -3.18 to -1.87).

We therefore conducted a sensitivity analysis (Supplementary Material, S6) by excluding this latter trial: heterogeneity decreased ($I^2 = 0.00\%$), but the overall results did not appreciably change (N = 2649; SMD = -0.04 ; 95% CI = -0.12 to 0.04) although this allowed to increase the certainty of such evidence to 'moderate', with the only serious concerns remaining for indirectness. To further check the robustness of our findings, we performed a subgroup analysis (Supplementary Material, S7) only on those seven trials with a similar population of patients with baseline dyslipidaemia (Carlsson et al., 2002; Gengo et al., 1995; Muldoon et al., 2000; Santanello et al., 1997; Stewart et al., 2000; Visseren et al., 2001; Wardle et al., 1996): again, outcome data consistently showed a non-significant difference between study arms (N = 2386; SMD = -0.03 ; 95% CI = -0.12 to 0.05), but the certainty of evidence could be upgraded to 'high'. Finally, to explore for potentially different effects between lipophilic and hydrophilic statins, we conducted another sensitivity analysis by excluding data measured for hydrophilic statins (Supplementary Material, S8), but results remained consistently non-significant (N = 1497; SMD = -0.29 ; 95% CI = -0.62 to 0.03 ; 'very low' certainty).

Comparable results were observed at all timepoints considered (Supplementary Material, S9): early (<6 months; N = 282; SMD = -0.09 ; 95% CI = -0.33 to 0.15 ; low certainty), medium (6–12 months; N = 1799; SMD = -0.38 ; 95% CI = -0.84 to 0.08 ; very low certainty), and late (>12 months; N = 1761; SMD = 0.06 ; 95% CI = -0.16 to 0.03 ; high certainty).

Three trials (Hyyppä et al., 2003; Morales et al., 2006; Sheridan et al., 2014) reported data that could not be pooled for this outcome measure because no adequate summary statistics was provided for each study arm. Hyyppä et al., (Cheng et al., 2016) found a negative effect of simvastatin on depressive symptoms (N = 120; mean difference = 0.06 ; standard error = 0.03 , $p = 0.016$). Also Morales et al., (Page et al., 2021) observed a higher number of people taking statins versus placebo (4/31 vs 1/34) with a score in keeping with a diagnosis of depression. Conversely, the study by Sheridan et al., (Harrison and Ashton, 1994) did not identify any statistically significant effect of fluvastatin on depressive scores (N = 50; mean difference = -0.11 ; standard error = 0.76 ; $p = 0.886$).

3.5. Acceptability, tolerability

Treatment acceptability (Fig. 3) did not differ between the statin and control groups (N = 2446; RR = 0.99 ; 95% CI = 0.85 to 1.15 ; moderate certainty), with no heterogeneity.

Treatment tolerability (Fig. 4) was slightly worse for the statin group, but this difference was not statistically significant (N = 1193; RR = 1.20 ; 95% CI = 0.79 to 1.82 ; moderate certainty), and no heterogeneity was identified.

Two trials (Muldoon et al., 2000; Santanello et al., 1997) reported data that could not be pooled for these outcome measures as the number of participants discontinuing treatment was not divided per study arm. Muldoon et al., (Carlsson et al., 2002) said that 15 participants withdrew, of which one due to an adverse drug reaction (rash), out of the 209 randomised. Similarly, Santanello et al., (Gengo et al., 1995) described that 55 participants withdrew, of which 16 due to adverse events, out of the 431 randomised.

3.6. Safety

Adverse events were inconsistently reported among trials (Supplementary Material, S10). For participants experiencing any adverse events (N = 289; RR = 1.07 ; 95% CI = 0.66 to 1.73 ; moderate certainty) and suicides (N = 1398; RR = 0.64 ; 95% CI = 0.17 to 2.45 ; very low certainty), pooled estimates were not statistically significant, with large confidence intervals due to the very low number of events reported, and no evidence of heterogeneity. For self-harm, no events were observed in any of the included trials for either arm, so these data were not pooled according to guidelines (JPT et al., 2021).

Five trials (Carlsson et al., 2002; Robertson et al., 2017; Santanello

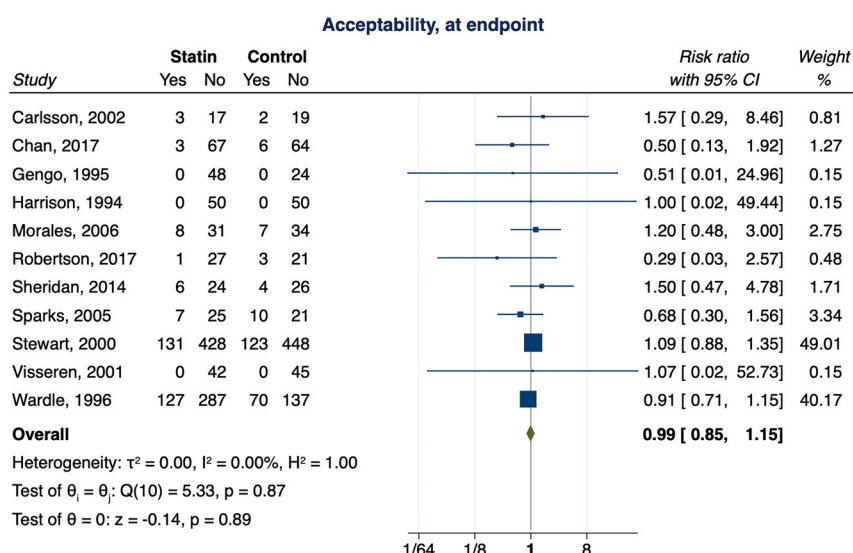


Fig. 3. Forest plot for acceptability (number of participants discontinuing treatment due to any cause).

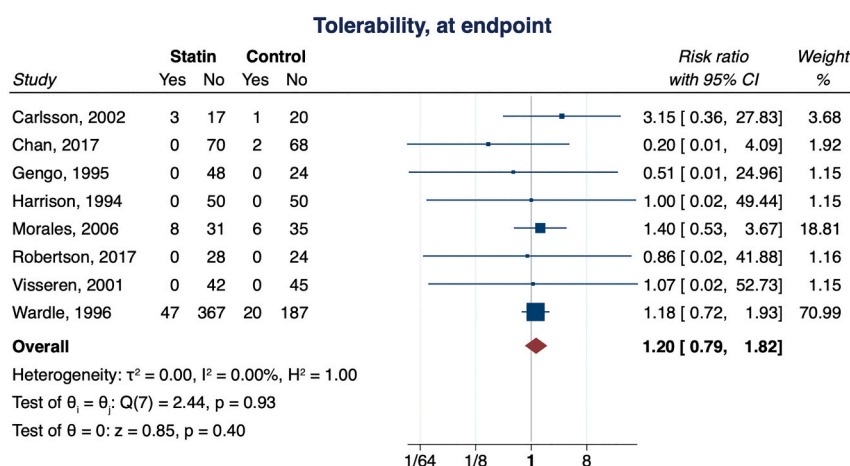


Fig. 4. Forest plot for tolerability (number of participants discontinuing treatment due to adverse events).

et al., 1997; Sheridan et al., 2014; Wardle et al., 1996) reported the total number of adverse events per study arm: overall, 4750 adverse events were reported over 742 participants on statins versus 2389 adverse events over 408 participants in the control groups.

4. Discussion

In this systematic review and meta-analysis, we investigated the putative antidepressant effects of statin monotherapy in adults over the available randomised controlled trials. Overall, we found no evidence that statins, without concurrent antidepressant treatment, have a significant advantage over placebo in reducing depressive symptoms in the general population. This result remained consistent at all timepoints considered and after sensitivity and subgroup analyses, thus increasing our confidence in its validity. Likewise, none of the secondary outcomes, namely acceptability, tolerability, and safety showed any difference between treatment with statins or placebo.

On the surface, our negative findings for efficacy appear in contrast with the positive results of several previous meta-analyses of randomised controlled trials (Yatham et al., 2019; Lee et al., 2021a; Köhler-Forsberg et al., 2019). These earlier studies had all included, among others, three positive trials where statins had been given in add-on to antidepressants in patients explicitly diagnosed with depression (Ghanizadeh and Hedayati, 2013; Gougol et al., 2015; Haghighi et al., 2014). Indeed, other meta-analyses that focussed on these specific intervention and population had highlighted the benefit of treating depressed participants by combining statins and antidepressants (De Giorgi et al., 2021a; Bai et al., 2020; Salagre et al., 2016). Our current work excluded instead trials investigating add-on antidepressant strategies; nevertheless, our more homogeneous study sample was larger than earlier ones as our comprehensive search strategy retrieved several trials that had escaped previous meta-analyses.

Some epidemiological evidence has suggested that statin-users may have a lower risk of incident depression compared to non-users irrespective of concurrent antidepressant use (Molero et al., 2020; Kessing et al., 2019). However, this benefit was not observed in a more recent meta-analysis of observational studies (Lee et al., 2021b), and likewise we have not been able to replicate such positive findings in a study we have recently conducted on a UK-based primary care database (unpublished data). By contrast, the same investigation in depressed patients taking an antidepressant showed that those taking a statin as add-on had better psychological and physical health outcomes, though only a small non-significant effect was noted in terms of lowering depressive scores (unpublished data).

Taken together, these data seem to suggest that statins, rather than being antidepressant molecules per se, might be usefully employed as an

augmentation strategy with conventional antidepressants for the management (i.e., treatment and/or relapse prevention) of people with depression. Indeed preliminary evidence has hinted at a possible interaction of statins with BDNF receptor systems critical to antidepressant response (Casarotto et al., 2021). The biological, psychological, and clinical underpinnings of such complex add-on effects are not known, but deserve further examination for their inherent translational value. Novel mechanisms behind mood regulation or antidepressant action might be explored by using statins as a versatile investigative tool in view of their ability to probe numerous physiological processes (Walker et al., 2021; Kosowski et al., 2021). Conversely, statins may have clinically meaningful effects in depression by acting on specific psychopathological domains, such as anxiety or anhedonia (De Giorgi et al., 2021c) and cognitive function (Massardo et al., 2022), effects which are not necessarily captured with sufficient sensitivity by commonly-used clinical scales for depression. Nevertheless, such therapeutic effects, if compounded by those of conventional antidepressant medication, could lead to an overall greater functional benefit on the depressive syndrome. Larger clinical trials (Husain et al., 2019; Otte et al., 2020) are nonetheless still necessary before endorsing statins add-on use for the treatment of depression.

Our findings for acceptability, tolerability, and safety are more difficult to contextualise as we could not identify any equally designed study that had specifically assessed these outcomes. Two studies previously mentioned had shown that antidepressant treatment dropouts and adverse events were similar in the short term (De Giorgi et al., 2021a) or indeed fewer during longer treatment periods (unpublished data) when statins were combined with antidepressants as compared to antidepressants alone. These results would not be directly comparable to our present ones exploring the effects of statin monotherapy, but on the whole confirm the established safety profile of statins over the wide follow-up range (i.e., 4 to 152 weeks) included in the current meta-analysis.

4.1. Limitations

This study has a number of limitations.

Although our search was extensive and queried several databases, there may still be trials that could have been missed. This issue might however be marginal as demonstrated by the lack of evidence for publication bias as well as the inclusion of many studies that were not retrieved in other recent systematic reviews.

Compared to the latter, we strived for a more uniform study population by excluding previously included trials that had investigated the use of statins plus antidepressants versus antidepressants alone in patients with a diagnosis of depression, as we believe that these studies

answer a different clinical and research question about the value of statin as add-on therapy in depressed patients. However, we still pooled data from a variety of participants with very different background diagnoses and comorbidities. Baseline presence of depressive disorders and antidepressant use, though likely low or even specifically excluded, were inconsistently described – which may have introduced bias. On the other hand, the inclusion of a more varied population increases results' generalisability. We were reassured by our analysis within the larger subgroup of patients with dyslipidaemia, whose findings were consistent with our primary outcome ones. However, it remains possible that other subgroups of patients may be more liable to show a better (or worse) effect on depressive symptoms of statins given in monotherapy – something that could have gone unnoticed in certain studies because of low sample sizes and thus lack of sufficient power.

In this regard, the trial by Sparks et al., (Sparks et al., 2005) was a noteworthy outlier as it found a strong antidepressant effect of atorvastatin monotherapy in people with mild-to-moderate Alzheimer disease. Indeed, a precision approach to future clinical trials would see the a priori selection of target populations expected to respond to a specific intervention: for example, in the case of medications with an anti-inflammatory potential such as statins, populations with raised inflammatory markers (e.g., C-reactive protein), background inflammatory conditions (e.g., obesity), or an inflammatory phenotype of depression (e.g., prominent anxiety and anhedonia) should be considered (Miller et al., 2017). Equally, the underlying metabolic profile of the study participants is likely to play a major role also (Jones et al., 2021).

On a similar note of precision, it is also plausible that individual statins might differentially elicit an antidepressant response according to their lipophilicity and thus brain penetrance (Redlich et al., 2014) – something that we did not fully investigate in this pairwise meta-analyses. Our sensitivity analysis excluding those data that had measured the effects of hydrophilic statins did not steer our efficacy findings; however, only a network meta-analysis could rank among different statins (De Giorgi, 2019) and potentially identify a step-wise antidepressant effect according to lipophilicity. Some available network meta-analyses have shown conflicting results (De Giorgi et al., 2021a; Lee et al., 2021a), but this might be due again to the mixing of study populations and interventions under examination (De Giorgi et al., 2021b). A network meta-analysis of the more homogeneous trials hereby included could shed some light on this matter.

Finally, our evaluation of the trials' risk of bias and the grading of pooled evidence may have been more lenient than commonly advised (JPT et al., 2021). For instance, we chose not to consider the lack of a pre-specified protocol as something that would put the trial at overall high risk of bias because many studies were old, protocol registration was not in practice at the time, and the lack of it is unlikely to have led the study authors to report non-significant results. On the whole, the reasoning behind the quality assessment was discussed in depth and eventually agreed among study authors, then described in full in the relevant tables (Supplementary Material, S2 and S3). Aside that, our methodology and statistical analysis, as per pre-registered protocol, were robust and followed the recommended guidelines for systematic reviews which, along with low heterogeneity for most outcomes, support the validity of our results.

5. Conclusion

Evidence from this systematic review and meta-analysis does not support the antidepressant efficacy of statin monotherapy in the general population. Meanwhile, data about the use of statins as add-on treatment to antidepressants appear more promising and warrant further research investment.

CRedit authorship contribution statement

RDG, GR, PJC, and CJH conceived and designed the study. RDG,

NRP, and SW performed the literature search, and extracted the data. RDG wrote the first draft of the paper, NRP and SW devised the figures and tables. GR, PJC, and CJH supervised the study. All authors contributed to manuscript revision, read, and approved the submitted version.

Declaration of competing interest

CJH has received consultancy fees from P1vital, Lundbeck, Servier, UCB, Zogenix, J&J, and Syndesi outside of the current work. GR has been a speaker and/or consultant from Angelini, Janssen, Lundbeck, and Otsuka outside of the current work. The other authors declare that they have no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jad.2022.05.113>.

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