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Impact of statins on depression and suicidality: a systematic review

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Systematic Review

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Abstract

Statins have been proposed for repurposing in depression, but previous meta-analyses reported heterogeneous results and seldom addressed suicidality. We systematically reviewed the association of statin treatment with the risk of depression, depressive symptom severity and suicidality. We searched 3 databases (Embase, PsycINFO and PubMed) up to 31 March 2026 for observational and interventional studies in predominantly adult populations, published in English or French. Risk of bias and methodological quality were assessed with RoB 2 for randomised controlled trials (RCTs) and the NIH/NHLBI tools for observational studies. Results were synthesised by design, outcome and sample size. Sixty studies were included (9 cross-sectional, 38 longitudinal and 13 RCTs; 20 to over 4.6 million participants), 55 assessing depression and 11 suicidality. Observational associations were heterogeneous: generally modest in large general-population studies, mainly inverse in disease-specific populations, but discordant after stroke and traumatic brain injury. Larger antidepressant effects of adjunctive statins were reported in small single-centre RCTs. In contrast, the two largest trials in major depressive disorder, both at low risk of bias, yielded estimates close to zero. No consistent association with suicidality was observed, and no trial showed a significant worsening of mood. This systematic review updates and extends previous meta-analyses on statins. Observational results were heterogeneous. Lower suicide mortality was observed in two cohorts, but the largest study found no association with suicidal behaviour. Larger antidepressant effects were confined to small single-centre trials. Current evidence therefore does not support prescribing statins for antidepressant or suicide-preventive purposes.

Introduction

Depression is one of the most common mental disorders and a major public health issue. It affects more than 200 million people and ranks among the leading causes of disability(GBD 2023 Mental Disorder Collaborators, 2026). Suicide is one of its most serious complications, with more than 727,000 deaths worldwide in 2021, and is the third leading cause of death among people aged 15 to 29 years(GBD 2021 Suicide Collaborators, 2025). A substantial proportion of patients have an insufficient response to conventional antidepressants. Treatment-resistant depression is often stated to affect approximately 30% of persons receiving antidepressant treatment, but prevalences in real-world studies varied between 6 and 55%(McIntyre et al., 2023).

Several studies have highlighted lipids as promising biomarkers in psychiatry. Indeed, lipid metabolism is altered in various psychiatric disorders (Persons and Fiedorowicz, 2016; Wei et al., 2020). A meta-analysis including 65 studies found an inverse association between total cholesterol, LDL cholesterol and suicidality(Wu et al., 2016). However, in patients with bipolar disorders, a meta-analysis including 11 studies found no evidence for an association between plasma lipids and suicide attempts, but only 1 study was on outpatients (Bartoli et al., 2017). Recently, we analysed a cohort of more than 3000 patients with bipolar disorders and found that total cholesterol and LDL cholesterol were positively associated with suicidal ideation and suicide attempts(Frajerman et al., 2026).

If the association between plasma cholesterol and suicidal behaviours is real, lipid-modifying medications could have an impact on suicidal behaviours. Statins, widely prescribed for cardiovascular prevention, are potential candidates(De Giorgi et al., 2023b). By lowering cholesterol, statins could have opposite effects on mood. Reduced brain cholesterol might decrease central serotonergic activity, notably through the 5-HT1A receptor, and impair mood and impulse control. Conversely, modulation of membrane lipid rafts and monoaminergic signalling, along with cholesterol-independent anti-inflammatory, antioxidant, and neurotrophic effects, could be beneficial. None of these pathways has been causally established in humans (De Giorgi et al., 2023b). Lipophilic statins (e.g., simvastatin, atorvastatin, lovastatin) are thought to cross the blood-brain barrier more readily than hydrophilic statins (pravastatin, rosuvastatin), so that their central effects may differ(Lee et al., 2021a).

Previous meta-analyses have yielded heterogeneous results. In observational studies, a meta-analysis (7 studies, 9 187 patients) found a 32% lower risk of depression among statin users ([aOR] 0.68; 95% confidence interval [CI] 0.52–0.89)(Parsaik et al., 2014), whereas a more recent meta-analysis of 13 observational studies found a weaker association ([OR] 0.85; 95% CI 0.72–0.99) that was no longer significant after trim-and-fill adjustment for funnel-plot asymmetry (OR 0.87; 95% CI 0.74–1.02)(Lee et al., 2021b). In randomised controlled trials (RCTs), statins added to antidepressants showed moderate efficacy in major depressive disorder (SMD= -0.48; 95% CI -0.74 to -0.22 at 8 weeks)(De Giorgi et al., 2021a), with a possible advantage of high-dose atorvastatin in a network meta-analysis (Lee et al., 2021a), whereas statin monotherapy did not improve depressive symptoms (11 trials, 2 712 participants; standardised mean difference − 0.18; 95% CI -0.41 to 0.04)(De Giorgi et al., 2022).

These meta-analyses date from 2014 to 2022; new observational and randomised studies have since been published with sometimes discordant results, and suicidality has been far less explored than depression. We therefore conducted an updated systematic review, integrating observational and interventional evidence, of the impact of statin treatment on the risk of depression, the severity of depressive symptoms and suicidality (suicidal ideation, suicide attempts and suicide deaths).

Experimental Procedures

Eligibility criteria

Studies of adults were eligible regardless of comorbidities; studies including participants aged 15 years and over were retained when the sample was predominantly adult. The exposure was statin treatment, all molecules combined. The registered comparator was placebo for randomised trials. Because the registration also allowed non-randomised studies, the comparator in these studies was no statin treatment, including statin-unexposed periods in self-controlled designs and untreated control arms in open-label trials. Outcomes were the risk of depression (ascertained by diagnostic interview, rating scale, diagnostic codes or antidepressant dispensing), the severity of depressive symptoms on validated scales, suicidal ideation, suicide attempts and suicide deaths. Observational (cross-sectional, cohort and case-control) and interventional studies published in English or French were eligible; case reports,

preclinical studies, reviews and editorials were excluded. As planned at registration, studies were grouped by design (cross-sectional studies, longitudinal studies and RCTs) and by outcome (depression or suicidality).

Search strategy

Embase, PsycINFO and PubMed were searched without date restriction and were last searched on 31 March 2026. Only published studies were sought. The search equation combined terms related to statins, depression and suicidality and was developed with the assistance of the Université Paris Cité Libraries; the full strategies are provided in Supplementary Table 1. The reference lists of included articles were also screened.

Study selection and data extraction

Two reviewers (TC and LC) independently selected studies, blinded to each other's decisions, using the Rayyan software(Ouzzani et al., 2016), first on titles and abstracts, then on full texts; disagreements were resolved by a third reviewer (AF). Data extraction followed the same blinded, duplicate procedure using a standardised spreadsheet, and study authors were not contacted. Extracted data included design, setting, population, statin(s) and dose, numbers of participants and of exposed participants, follow-up, outcome instruments, and effect estimates with confidence intervals. All reported results were extracted for each outcome, including subgroup results by sex, age, molecule or dose; when several estimates were available, the main adjusted estimate in the total population was presented first. Missing or unclear information was recorded as not reported, without assumptions.

Quality assessment

Risk of bias in RCTs was assessed with the Cochrane RoB 2 tool (Sterne et al., 2019). We assessed the methodological quality of observational studies, including potential sources of bias, using the National Heart, Lung, and Blood Institute (NIH/NHLBI) study quality assessment tools [20]: the 14-item tool for cohort and cross-sectional studies and the 12-item tool for case-control studies. Assessments were performed independently and in duplicate by the same blinded reviewers, with arbitration by AF.

Effect measures and synthesis methods

Effect measures were reported as published (odds, risk, prevalence, hazard and incidence rate ratios; mean differences or standardised effect sizes), without conversion or imputation. A single quantitative synthesis was inappropriate because the included studies addressed different clinical questions, prevention in non-depressed populations; adjunctive treatment of major depressive disorder; experimental medicine; and specific medical populations, and differed in design, statin molecule, comparator, outcome definition, instrument, and follow-up (Deeks, 2024). Even among RCTs in major

depressive disorder, trials differed in population (newly diagnosed, severe, melancholic or treatment-resistant depression, comorbid obesity or youth), antidepressant co-treatment, rating scale and reporting format (means, medians, response rates or test statistics). We therefore conducted a structured narrative synthesis by design and outcome, emphasising the magnitude and precision of effect estimates, study size, population characteristics, and risk-of-bias judgements rather than statistical significance alone; we did not count votes(McKenzie, 2024). We tabulated results separately for observational studies of depression (Table 1), RCTs (Table 2), and studies of suicidality (Table 3), ordered by design and decreasing sample size, as the registration record planned to account for sample size. Heterogeneity was explored informally across populations, sample sizes and risk-of-bias judgements and, in exploratory analyses, across molecules, lipophilicity and doses.

Differences between registration and review

The review was registered on 29 May 2026, after completion of the search and screening but before data extraction. Although the registration specified adults, studies including participants aged 15 years and over were retained when the sample was predominantly adult. Three studies without a statin-free comparator, a head-to-head trial of simvastatin versus atorvastatin(Abbasi et al., 2015), a cohort comparing lipophilic with hydrophilic statins (Dave et al., 2018) and a cross-sectional study comparing statin doses(Pannir et al., 2025), were retained because they inform differences between molecules and doses; they are reported separately and were not used to assess the effect of statins versus no statin. Analyses by molecule, lipophilicity and dose were not pre-specified and are exploratory. The planned assessment of risk of bias due to missing results was not performed.

Results

Study selection and characteristics

The literature search was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline (Fig. 1). In summary, the search identified 834 records (PubMed 316, Embase 417, PsycINFO 101). After removal of 270 duplicates, 564 records' titles and abstracts were screened by applying the inclusion/exclusion criteria previously described, and 500 were excluded. Of the 64 reports sought for retrieval, three could not be retrieved; of the 61 reports assessed in full text, one was excluded because it was a protocol only. No additional study was identified through reference lists.

Sixty studies were included: 9 cross-sectional studies, 38 longitudinal studies (34 cohort and 4 nested case-control studies) and 13 RCTs (Tables 1–3). Fifty-five studies examined depression, six of which also reported suicidality outcomes, and five examined suicidality only. Studies were published between 1998 and 2026, and sample sizes ranged from 20(Massardo et al., 2022) to more than 4.6 million

participants(Redlich et al., 2014). Trials lasted 7 days to 12 weeks, whereas observational follow-up extended up to 18 years.

Depression: cross-sectional studies

In the largest study, of 1.35 million Austrians, statin use was associated with a higher prevalence of diagnosed depression (OR 1.22; 95% CI 1.20–1.25), with lower odds at low doses and higher odds at high doses(Leutner et al., 2021). Inverse associations were found in adults with cardiovascular disease in the Norwegian HUNT study, in men in both waves and in women in the more recent one(Bojanić et al., 2022), in adults with diabetes, strengthening with longer use(Li et al., 2024), and in adults aged 55 years and over (aOR 0.71; 95% CI 0.52–0.97)(Feng et al., 2008). No overall association was found in more than 19 000 adults aged over 70 years (aOR 1.09; 95% CI 0.98–1.20), with directions varying by age and body mass index(Agustini et al., 2019). In Italian older adults, depressive symptom scores were higher among statin users. However, the association with depression was not significant(Mandas et al., 2014), and it differed by ethnic origin in a UK tri-ethnic population, with no significant subgroup effects(Williams et al., 2015).

Depression: longitudinal studies

In the general population, results were mixed and effects modest. Lower risks among statin users were found in the Swedish total-population cohort, using a within-individual design that removes time-invariant confounding (adjusted hazard ratio [aHR] 0.91; 95% CI 0.87–0.94)(Molero et al., 2020), in a large UK cohort (aHR 0.87; 95% CI 0.81–0.94)(Yang et al., 2024) and in a Danish registry study comparing continued use with a single prescription (aHR 0.61 with 30 to 39 prescriptions)(Kessing et al., 2019), and slightly lower odds were found in Swedish adults aged 40 years and over(Redlich et al., 2014). Conversely, no association was found in a Danish propensity-matched cohort (adjusted hazard rate ratio 1.07; 95% CI 0.99–1.15)(Köhler-Forsberg et al., 2019), in a Swiss population-based cohort(Glaus et al., 2015) or in a self-controlled case series (adjusted incidence rate ratio [aIRR] 0.95; 95% CI 0.87–1.04)(Ye et al., 2023).

In patients with depression, two very large English primary care cohorts found no association between adjunctive statins and response or remission. However, psychometric data were missing for nearly 80% of patients(De Giorgi et al., 2024, 2023a), whereas statin use was associated with a lower risk among new users of selective serotonin reuptake inhibitors (SSRIs) in Denmark (aHR 0.64; 95% CI 0.55–0.75) (Köhler et al., 2016).

Lower risks were mainly observed in populations defined by a somatic disease: after an acute coronary syndrome(Wium-Andersen et al., 2017a) or a stroke (Kim et al., 2014; Wium-Andersen et al., 2017b), in coronary heart disease (Otte et al., 2012; Stafford and Berk, 2011; Young-Xu et al., 2003), hyperlipidaemia(Chuang et al., 2014) and asthma-chronic obstructive pulmonary disease overlap syndrome(Yeh et al., 2019), and after traumatic brain injury (Chen et al., 2023; Khokhar et al., 2018). Findings were nevertheless discordant within the same neurological populations, with higher risks among statin users after stroke (aHR 1.59; 95% CI 1.30–1.95)(Kang et al., 2015) and after traumatic

brain injury (hazard ratio [HR] 1.91; 95% CI 1.79–2.04)(Lin et al., 2026). No significant association was found after intensive care(Medici et al., 2017), during the COVID-19 lockdown(Gillespie et al., 2022), in patients with an implantable cardioverter-defibrillator(Hoogwegt et al., 2013), or in patients with head and neck cancer(Huang et al., 2017), and the direction varied by sex in older adults(Feng et al., 2010).

In nested case-control studies, statin use was associated with lower odds of depression in a general population without psychiatric history(Yang et al., 2003) and of mood disorders in men(Williams et al., 2016), but not significantly in women(Pasco et al., 2010), the latter two estimates relying on very few exposed cases. A prescription sequence symmetry analysis(Lindberg and Hallas, 1998) and a small pilot study(Krysiak et al., 2018) found no significant association.

Depression: randomised controlled trials

The two largest trials, both at low risk of bias, yielded estimates close to zero: simvastatin added to escitalopram in depression with obesity (n = 160; adjusted difference on the Montgomery-Åsberg Depression Rating Scale [MADRS] 0.47; 95% CI -2.08 to 3.02)(Otte et al., 2025) and adjunctive simvastatin in treatment-resistant depression (n = 150; adjusted MADRS difference − 0.61; 95% CI -3.69 to 2.46)(Husain et al., 2023). In young people with moderate to severe depression, rosuvastatin was associated with a 4.2-point lower MADRS score, with a wide confidence interval including no difference (n = 130; 95% CI -9.1 to 0.6)(Berk et al., 2020), and in healthy volunteers at risk of depression, simvastatin showed no group-by-time interaction (n = 101)(Giorgi et al., 2025); both trials were also at low risk of bias. Larger effects were reported in smaller single-centre augmentation trials in major depressive disorder (44 to 68 participants, 6 to 12 weeks), with lovastatin plus fluoxetine(Ghanizadeh and Hedayati, 2013), atorvastatin as add-on therapy(Aldossary et al., 2024), atorvastatin plus citalopram(Haghighi et al., 2014) and simvastatin plus fluoxetine(Gougol et al., 2015): response rates reached 73% versus 44% with atorvastatin in the per-protocol analysis(Aldossary et al., 2024) and 90% versus 59% with simvastatin (Gougol et al., 2015). Lovastatin produced a 4.6-point greater reduction in Hamilton Depression Rating Scale scores than placebo (Ghanizadeh and Hedayati, 2013). The other trials showed no between-group difference: a secondary analysis not designed for depression(Fotso Soh et al., 2020), an open-label pilot trial in hepatitis C with few depressed participants (Sheridan et al., 2014), a seven-day study in healthy volunteers(De Giorgi et al., 2021b) and a 20-patient trial in melancholic depression(Massardo et al., 2022). No trial reported a significant worsening of mood.

Molecule, lipophilicity and dose (exploratory analyses)

Three studies without a statin-free comparator addressed molecules or doses: simvastatin reduced Hamilton Depression Rating Scale scores more than atorvastatin after coronary artery bypass grafting (mean difference 3.63; 95% CI 0.44–6.51)(Abbasi et al., 2015), lipophilic and hydrophilic statins did not differ overall in a propensity-matched cohort (aHR 1.05; 95% CI 1.00-1.10)(Dave et al., 2018), and the prevalence of depression did not differ between doses in patients with diabetes(Pannir et al., 2025). Placebo-controlled trials could not compare lipophilic and hydrophilic statins, as all but two used lipophilic molecules; the two rosuvastatin trials showed a non-significant trend(Berk et al., 2020) and no

between-group difference(Massardo et al., 2022), and the two largest trials, with estimates close to zero, used simvastatin(Husain et al., 2023; Otte et al., 2025). Observational data were contradictory, simvastatin being associated with a higher risk of depression in a prescription sequence symmetry analysis (adjusted relative risk 1.59)(Lindberg and Hallas, 1998) and a propensity-matched cohort (HR 1.09) (Dave et al., 2018), but with a lower risk in a Swedish national cohort (OR 0.93)(Redlich et al., 2014). Within a Medicare cohort after traumatic brain injury, risk reductions were similar for lipophilic and hydrophilic statins (aRR 0.81 for atorvastatin, 0.88 for simvastatin, 0.84 for pravastatin and 0.83 for rosuvastatin)(Khokhar et al., 2018). Dose and duration findings were also heterogeneous: low doses were associated with a lower and high doses with a higher prevalence of depression in Austria(Leutner et al., 2021), and only low doses with a lower risk of post-stroke depression in patients treated with repetitive transcranial magnetic stimulation(Cui et al., 2025), whereas longer or more continuous use was associated with greater risk reductions(Kessing et al., 2019; Li et al., 2024).

Suicidality

The largest cohort (1 149 384 individuals) found no association: the Swedish within-individual estimate for suicidal behaviour or suicide death was null (aHR 0.99; 95% CI 0.90–1.08)(Molero et al., 2020), as was the self-controlled case series for suicide attempts (aIRR 0.87; 95% CI 0.72–1.06)(Ye et al., 2023). No significant association was found among new SSRI users (aHR 0.85; 95% CI 0.61–1.18)(Köhler et al., 2016), in English primary care(De Giorgi et al., 2024), between lipophilic and hydrophilic statins(Dave et al., 2018), or in nested case-control studies of suicidal behaviour (Yang et al., 2003) and completed suicide(Callréus et al., 2007).

Two cohorts found lower suicide mortality among statin users, in Finland (aHR 0.53; 95% CI 0.43–0.65) (Haukka et al., 2012) and in patients with bipolar disorder (aHR 0.51; 95% CI 0.34–0.78)(Chen et al., 2025); a methodologically comparable cohort of patients with schizophrenia found a similar but imprecise estimate (aHR 0.57; 95% CI 0.25–1.30)(Chen et al., 2024). Only one small cross-sectional study reported more suicidal ideation among users of lipophilic statins (prevalence ratio 2.59; 95% CI 1.27–5.31)(Davison and Kaplan, 2014).

Risk of bias and methodological quality

Of the 13 trials, 6 were at low risk of bias, 6 raised some concerns, mainly regarding randomisation, deviations from intended interventions and selection of the reported result, and the open-label trial was at high risk(Sheridan et al., 2014)(Supplementary Fig. 1). Among the trials reporting larger effects, only one was at low risk of bias(Haghighi et al., 2014), whereas the four trials with 100 or more participants were all at low risk(Berk et al., 2020; Giorgi et al., 2025; Husain et al., 2023; Otte et al., 2025). Of the 47 observational studies, 26 were of good quality, 16 fair and 5 poor (Supplementary Figs. 2–4). Sample size justification was the item most often unmet; cross-sectional studies by design failed the temporality items, and the NIH/NHLBI tools do not assess confounding by indication.

Discussion

This systematic review of 60 studies found that statins' impact depends on the population studied and the effect sought. Larger antidepressant effects of adjunctive statins in major depressive disorder were confined to small single-centre trials. In contrast, the two largest trials, at low risk of bias, yielded estimates close to zero, and small trials in non-depressed individuals showed no preventive effect. The concentration of larger effects among smaller trials is compatible with a small-study effect. However, this cannot be distinguished from other sources of between-study heterogeneity or from publication and selective-reporting bias. It overlaps with risk of bias, as only one trial reporting larger effects was at low risk(Haghighi et al., 2014).

The trials reporting larger effects share other features that limit their weight. They were short (6 to 12 weeks), used the Hamilton scale as the primary outcome and were all conducted in Iran or Egypt, which calls for independent replication(Aldossary et al., 2024; Ghanizadeh and Hedayati, 2013; Gougol et al., 2015; Haghighi et al., 2014). Differences in populations are unlikely to explain the discrepancy entirely, since the largest trial, with an estimate close to zero, also combined a statin with a selective serotonin reuptake inhibitor in major depressive disorder(Otte et al., 2025). In contrast, the other large trials enrolled patients with treatment-resistant depression(Husain et al., 2023), young people(Berk et al., 2020) or healthy volunteers(Giorgi et al., 2025).

The lipophilicity hypothesis could not be adequately tested, as the analysis was exploratory; almost all trials used lipophilic statins. The available data did not favour lipophilic statins, however: the two largest trials, with estimates close to zero, used simvastatin, a highly lipophilic statin (Husain et al., 2023; Otte et al., 2025); lipophilic and hydrophilic statins did not differ in a propensity-matched cohort (Dave et al., 2018) and were associated with similar risk reductions after traumatic brain injury (Khokhar et al., 2018); and observational findings for simvastatin were contradictory(Dave et al., 2018; Lindberg and Hallas, 1998; Redlich et al., 2014).

Pathophysiological hypotheses

Interestingly, the lack of clinical effect contrasted with expected reductions in low-density lipoprotein (LDL) cholesterol, total cholesterol, and C-reactive protein in an obese population with low-grade inflammation, making poor adherence or an inappropriate population unlikely(Otte et al., 2025). A similar dissociation between within-group or indirect improvement and the absence of between-group difference was observed in two other trials (De Giorgi et al., 2021b; Massardo et al., 2022). This suggests that peripheral lipid-lowering and anti-inflammatory effects may not be sufficient to produce an antidepressant effect.

A review suggests that lipid rafts are a significant modulator of monoaminergic neurotransmission, influencing co-localisation of transporters/receptors with other signalling proteins and adaptor molecules; trafficking by endocytosis; agonist and antagonist binding; and downstream second messenger-mediated events(Liu et al., 2018). One hypothesis is that changes in membrane lipid raft structure, driven by the proportions of cholesterol and n-3 PUFAs (polyunsaturated fatty acids), affect the

function of membrane-bound proteins, including serotonin receptors and transporters, as well as toll-like receptors. More recently, a review suggested that decreased cholesterol levels in lipid rafts reduced levels of the lipid raft protein S100A10 (p11) and impaired anchoring of 5-HT1B and 5-HT4 receptors, resulting in less effective suppression of impulsive and aggressive behaviour (Kalkman and Smigielski, 2026). Statins affect fatty acid levels, possibly through their effects on desaturases [84–86], and can also increase the n-6:n-3 PUFA ratio, thereby promoting inflammation, since n-3 PUFAs tend to be anti-inflammatory and n-6 PUFAs tend to be pro-inflammatory. Abnormal monoaminergic neurotransmission and the presence of neuroinflammation are two major theories leading to biological pathways to suicide(Daray et al., 2018). A study on the UK Biobank found that higher n-3 PUFA levels were associated with reduced risks of self-harm and suicidal ideation(Franco et al., 2025).

Furthermore, a study found that the relationship between total unesterified cholesterol and suicide risk was significantly mediated by ABCA-1-specific cholesterol efflux capacity, suggesting that cholesterol metabolism and associated molecular pathways could be informative for understanding the neurobiological underpinnings of suicide (Knowles et al., 2018). Beyond cholesterol, sphingolipids, which together with cholesterol form lipid rafts(Liu et al., 2018), may also be involved in depression: several clinical studies have reported elevated ceramide levels correlating with depression severity, and many antidepressants act as functional inhibitors of acid sphingomyelinase or modulate this pathway indirectly (Hoertel et al., 2026).

A recent review suggests that some of the benefits observed with statins were not linked to cholesterol lowering but to the ability of statins to directly interact with and alter the physical properties of lipid membranes(Preta, 2026).

In schizophrenia, add-on simvastatin did not improve PANSS total score in a large randomised trial, although a meta-analysis of seven trials reported in the same article suggested a small benefit of statins(Weiser et al., 2023), suggesting statins' action could be on more than just suicide.

Statin safety

A reanalysis by the Cholesterol Treatment Trialists' Collaboration of individual participant data from 19 double-blind trials (123 940 participants) found that, of 66 unconfirmed adverse effects listed in product labels, only four were associated with statins, all somatic and of small magnitude, with no causal link with depression, cognitive impairment or sleep disorders(Cholesterol Treatment Trialists and Cholesterol Treatment Trialists, 2026). Consistently, no trial in our review showed a significant worsening of mood or suicidality, which supports the feasibility of dedicated trials in psychiatric populations.

Strengths and Limitations

Previous syntheses focused on a single study design and on depression alone(De Giorgi et al., 2022, 2021a; Lee et al., 2021a, 2021b; Parsaik et al., 2014). Our review brings together observational and interventional studies, includes suicidality and updates the evidence to 2026, including the two largest augmentation trials in depressed patients published to date(Husain et al., 2023; Otte et al., 2025). It thus

clarifies where an effect may lie (adjunctive statins in small trials) and where it does not (prevention in the general population and the best-powered trials).

The main limitation is heterogeneity in assessment instruments, populations, molecules, follow-up durations, and sample sizes, which makes quantitative pooling difficult to interpret(Deeks, 2024). Cross-sectional studies preclude causal inference; registry-based studies capture only diagnosed or treated depression; observational studies remain exposed to confounding by indication, which within-individual designs address only for time-invariant factors; and administrative data identify suicide deaths less accurately than suicide attempts(Snowdon and Choi, 2020). Although the two largest trials were at low risk of bias, they included only 150 and 160 participants; their 95% confidence intervals (− 3.69 to 2.46 and − 2.08 to 3.02 MADRS points) exclude large effects but not small ones.(Husain et al., 2023; Otte et al., 2025) Suicide attempts and deaths were rare outcomes, and several suicidality estimates were imprecise.

The review process also has limitations. The search was restricted to English and French publications. It did not include trial registries or grey literature, and risk of bias due to missing results was not assessed, so that publication bias cannot be excluded. In addition, our search terms may have missed older placebo-controlled trials in which depressive symptoms were a secondary outcome; such trials were pooled in a previous meta-analysis, which found no significant effect of statins on psychological outcomes (O'Neil et al., 2012), but improved mood scores in a sensitivity analysis of two trials (SMD − 0.43; 95% CI -0.61 to -0.24).

Lipids, statins and precision psychiatry

To date, the evidence does not support prescribing statins for antidepressant or suicide-preventive purposes, in the general population or psychiatric populations. Over the last few years, more studies have focused on precision psychiatry, validating new biomarkers, incorporating biological information into diagnostic classification, and developing new treatment strategies (Etkin et al., 2026; Kas et al., 2025).

Preclinical models could help to better understand the biological effects of statins(Rahangdale et al., 2021; Yu et al., 2024).

Future research should use high-resolution technologies such as mass spectrometry or nuclear magnetic resonance (NMR) to identify biomarkers of response. For instance, a few studies used NMR to identify lipoproteins associated with psychotic transition(Avella et al., 2025) and treatment-resistant schizophrenia(Marino et al., 2026).

Conclusion

This systematic review updates and extends previous meta-analyses on statins. Results from observational studies were heterogeneous. A lower suicide mortality was observed in 2 cohorts (general population and bipolar disorder patients) but not in all cohorts. Larger antidepressant effects of

adjunctive statins were confined to small single-centre trials, whereas the two largest trials, both at low risk of bias, found estimates close to zero. Current evidence therefore does not support prescribing statins for antidepressant or suicide-preventive purposes. More accurate preclinical and clinical studies are needed to better understand the central biological effects of statins and to identify patient subgroups that could benefit from statin treatment.

Declarations

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Author contributions

TC and LC performed study selection, data extraction and risk-of-bias assessment.

TC: Writing – original draft

LC: Writing – review & editing

AF resolved disagreements; Writing – original draft, Methodology, Conceptualisation. Supervision

NH: Writing – review & editing

All authors revised and approved the final version.

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Conflict of Interest

NH is co-founder and scientific director of CERAMED, a company developing sphingolipid-based diagnostics and therapeutics under the French PACTE law public-private partnership.

The other authors declare no conflict of interest.

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Tables

Tables 1 to 3 are available in the Supplementary Files section.

Figures

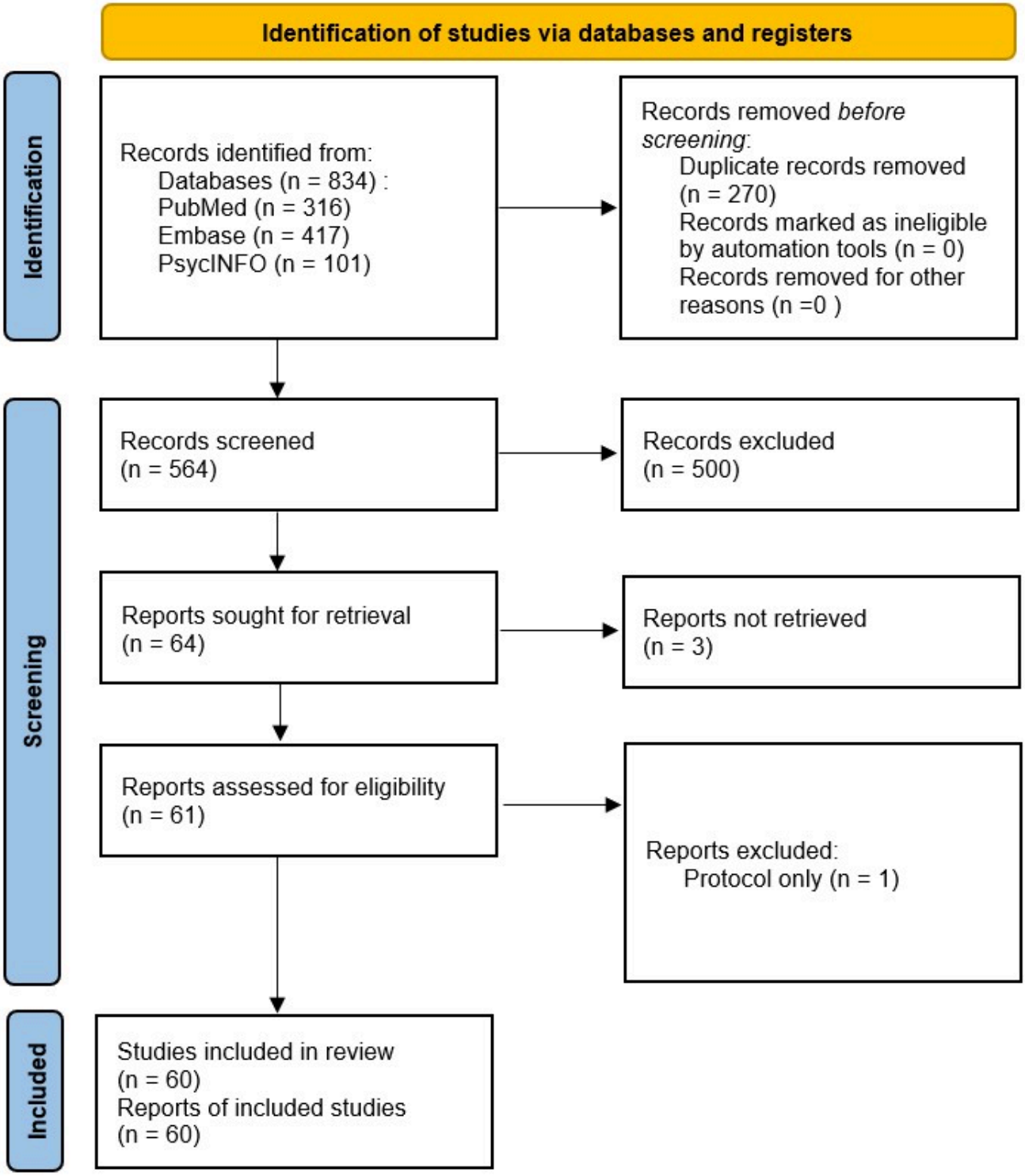


Figure 1

Flow Chart

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