# Manuscript Details

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**Abstract**

Background: Depressive disorders account for almost half of all Disability Adjusted Life Years caused by psychiatric disorders but efficacy of pharmacological interventions to prevent depressive disorders is not known. We aimed to assess efficacy of pharmacological treatments in prevention of depression. Methods: We searched PubMed, Psych Info, EMBASE, and CINHAL from 1980 to April 2018 and bibliographies of relevant systematic reviews. We selected randomised controlled trials (RCTs) that used pharmacological intervention to prevent the onset of a new depressive episode in adult population. Study selection, data extraction and reporting was done following PRISMA guidelines. Data were pooled using random-effects meta-analysis. Results: 28 trials (2745 participants) were included in meta-analysis. Antidepressants (22 studies), Selenium, Hormone Replacement Therapy Omega-3 fatty acids and Melatonin were used to prevent depression, mostly in physical conditions associated with high risk of depression. All pharmacological interventions [pooled Odds Ratios (OR) 0.37 CI (0.25-0.54)], and antidepressants (OR 0.29, 95% CI: 0.18, 0.46) were significantly more effective than placebo in preventing depression. Antidepressants were significantly better than placebo in trials that had low risk of bias (n=16; OR 0.43 [0.30, 0.60]), in preventing post stroke depression (OR=0.16, 95% CI: 0.05, 0.55) and depression associated with Hepatitis C (OR=0.56, 95% CI: 0.31, 1.02). Limitations include a small number of studies focussed on high risk conditions and short follow up periods. Conclusions: Prevention of depression may be possible in patients who have high-risk conditions but the strategy requires complete risk and benefits analysis before it can be considered for clinical practice.



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| **Keywords** | Key Words: Depression; depressive illness; prevention; drugs; pharmacological agents; meta-analysis. |



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## HIGHLIGHTS

- Systematic review and meta-analysis that includes all pharmacological interventions used in prevention of depression has not been published.

- We identified the following pharmacological interventions which were evaluated in 28 published studies: Antidepressants, Selenium, Hormone Replacement Treatment and Omega 3 fatty acids, Melatonin.

- All pharmacological intervention including antidepressants (evaluated in 22 of the 28 included studies) had a significant preventive effect on reducing the incidence of depression in high risk conditions.

- The Number Needed to Treat (NNT) for the preventive effect of all pharmacological intervention was seven. In the analysis limited to studies using antidepressants, the NNT was 6 and in studies with low risk of bias the NNT was 8.

- The use of prophylactic antidepressants generally had little effect on other relevant outcomes, such as disability.

- Although the effects were consistent across high quality trials and across different physical conditions, the acceptability of antidepressant treatment to prevent rather than treat the depression needs to be examined before the strategy can be considered for routine clinical practice.

## ABSTRACT

**Background:** Depressive disorders account for almost half of all Disability Adjusted Life Years caused by psychiatric disorders but efficacy of pharmacological intervention to prevent depressive disorders is not known. We aimed to assess efficacy of pharmacological treatments in prevention of depression.

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**Limitations** include small number of studies focussed only on high risk conditions and short follow up in most studies.

**Conclusions:** Prevention of depression may be possible in patients who have high-risk conditions such as stroke but the strategy requires complete risk and benefits analysis before it can be considered for clinical practice

**Key Words:** Depression, depressive illness, prevention, drugs, pharmacological agents, meta-analysis

**PHARMACOLOGICAL INTERVENTIONS FOR PREVENTION OF DEPRESSION IN HIGH RISK CONDITIONS: SYSTEMATIC REVIEW AND META-ANALYSIS.**

**Running Title**: Pharmacological interventions for depression prevention

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# PHARMACOLOGICAL INTERVENTIONS FOR PREVENTION OF DEPRESSION IN HIGH RISK CONDITIONS: SYSTEMATIC REVIEW AND META-ANALYSIS.


## ABSTRACT

**Background:** Depressive disorders account for almost half of all Disability Adjusted Life Years caused by psychiatric disorders but efficacy of pharmacological intervention to prevent depressive disorders is not known. We aimed to assess efficacy of pharmacological treatments in prevention of depression.

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## INTRODUCTION

The global burden of diseases study estimated that depressive disorders account for 40% of the Disability Adjusted Life Years (DALYS) caused by all mental and substance abuse disorders (Whiteford et al., 2013). It is estimated that even if the coverage, clinical competence and compliance become optimal with no major barriers to health service delivery and financing, only 36% of the total burden of disease caused by depressive disorders could be averted using current interventions and knowledge (Andrews et al., 2004). This situation demands that the prevention of depressive illness be a major health priority (Cuijpers et al., 2012).

Three types of preventive approaches have been used in prevention of depression (van Zoonen et al., 2014). The universal prevention focuses on the whole population group regardless of risk status (Spence et al., 2003). Selective prevention targets individuals who are at higher risk of developing a condition such as women during the postnatal period. Indicated prevention targets the individuals who are identified through biological markers to mental disorders, but who do not yet meet the diagnostic criteria for depressive illness (Muñoz et al., 2010). The pharmacological interventions for prevention of depression have mainly used the selective approach. These include focussing on the high risk groups such as those who are at higher risk to develop depression following physical conditions like hepatitis C, stroke or acute coronary syndrome (see below). This approach has the advantage that population at risk is already receiving medical care and thus relatively easy to identify and target.

The pharmacological treatment that can prevent the onset of depressive disorders would represent a major public health advance in averting the colossal burden caused by the illness, as the currently available pharmacological treatments are relatively cheap, are available universally and can be easily administered (Kupfer, 2005). The systematic reviews of the preventive strategies in depression have mainly focused on psychological interventions (Cuijpers et al., 2008). The pharmacological interventions for the prevention of depression have been systematically reviewed for specific categories such as Post-Natal Depression (Miller et al., 2013; Molyneaux et al., 2018). No systematic review and meta-analysis of all the pharmacological interventions used for prevention of depression is published.

We aim to identify and evaluate the efficacy of all pharmacological treatments that have been used for preventing the onset of depressive illness in adult populations.

## METHODS

### Outcome measures:

The primary outcome of interest for this review is the incidence of depressive disorders in the intervention group compared with the control group post-intervention and at follow-up. We used the incidence based on the diagnostic instrument that was specified as primary diagnostic instrument, as mentioned in the description of primary end point of each study. Where this was not clear, we preferred the interview based diagnosis over the diagnosis based on cut-off point of a scale.

Since majority of included trials were in patients with persisting physical conditions, we also report the effects of interventions on physical health outcomes, such as disability or the effect of prophylactic antidepressant treatment in response to anti-viral treatments.

**Data Sources and Searches**

The meta-analysis was done and is reported following the PRISMA guidelines for identification and selection of studies, data extraction and reporting (see the online appendix-1 for the PRISMA 2009 Checklist for reporting the article).

The search was performed in the electronic data bases PubMed, PsychInfo, EMBASE, and CINHAL, with the last updated search in January 2020. The search was limited to randomised controlled trials (RCT) published from 1980, since clinical trials based on diagnostic criteria relevant to this review did not exist before that time. Searches were conducted using the following search strings using both MeSH terms and text words: **"**depression" OR "antidepressants" OR "prevention" OR "preventing onset of depression" OR "preventing depressive episode(s)" OR "preventing depressive" OR "prevention" OR "prophylaxis"; "depression" AND "antidepressants" AND ("prevention" OR "preventing onset of depression" OR "preventing depressive episode(s)" OR "preventing depressive" OR "prophylaxis"). The following strings were applied to eliminate the articles related to preventing the relapse of depressive disorders: "maintenance therapy" OR "recurrent" OR "recurrence" OR "relapsed" OR "relapsing" OR "pre-existing" OR "pre-existing depression". We identified 15 potentially relevant systematic reviews (appendix-2) on prevention of depression, and hand searched their bibliographies for additional references.

**Study Selection**

We included studies with the following characteristic:

1. Published RCTs that included participants aged 18 years and above who were not suffering from a depressive illness or not taking any treatment for depression at the start of the trial.
2. A pharmacological intervention initiated at least in one arm of the trial with the aim of preventing the onset of the new depressive episode.
3. Studies reported at least one outcome measure related to the prevention of depression.

We adopted the definition of prevention as recommended by the Institute of Medicine Report (National Research Council (US) and Institute of Medicine (US) Committee on the

Prevention of Mental Disorders and Substance Abuse Among Children, Youth, and Young Adults: Research Advances and Promising Interventions, 2009). Primary prevention would include interventions aimed at reducing the incident cases only. We included studies that recruited participants with a previous history of depression, but who were not suffering from depression at the beginning of the trial. The onset of depressive illness was defined using standard diagnostic criteria, such as International Classification of Disease (ICD-10), or the Diagnostic and Statistical Manual (DSM), based on standardised clinical interview or using score above cut off point on standardised and valid rating scales.

The relapse prevention studies which evaluated the effectiveness of maintenance treatment to prevent the relapse of depressive illness were excluded. Studies that used herbal preparations were also excluded, as these are usually combination of different chemical entities and it is not possible to identify an active pharmacological agent.

Two reviewers (SF and MA) identified the relevant studies from the titles and abstracts and obtained the potentially relevant full-text articles. Both reviewers read these to decide whether they met the inclusion criteria. A consensus was reached after mutual discussion in case of disagreement.

**Data Extraction and Quality Assessment;**

Project Registration, data management, quality assessment and coordination amongst the author were done using Metabase, a web-based data management tool (https://meta.mediware.pro) developed and managed by MediWare Health Informatics. The authors have used the system for a number of previous meta-analyses (Singh et al., 2010). Metabase allows project-based authorisation and differential access to all necessary tools, including access to the study protocol, full text articles, and data items for project members. All data were entered on pre-specified forms built in Metabase.

Two authors (SF and SPS) extracted the following data items from the selected papers: diagnosis and diagnostic criteria, quality measures, specific details of arms of trials, including sample characteristics and baseline medications, names of intervention, and duration of treatment; data types and format, and names of scales; and pre-trial and post -trial outcome scores. Any disagreement on data extraction was resloved through mutual discussion between the authors who extracted the data.

**Quality assessment of included studies**

We used the Cochrane Collaboration tool for assessing the risk of bias in randomised trials (Higgins et al., 2011) that uses the following seven domains: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective outcome reporting and 'other' bias. These domains are classified as having high, low and unclear risk of bias. In the 'other' bias domain, we considered whether a validated instrument/measurement was used to ascertain that participants were free of depressive illness at the baseline, as the inadequate screening for depression at baseline could result in recruiting participants with depression, which could inflate the effect of the intervention.

The methodological quality of the selected trials was assessed independently by two authors (SF and SS). A study was classified as having low risk of bias if the following items were all categorized as having low risk of bias based on Cochrane Collaboration tool: random sequence generation, blinding of participants and personnel, blinding of outcome assessment and 'other' bias. If any of these items were categorized as high risk or unclear, the study was classified as having high risk of bias.

**Measures of treatment effect.** Where dichotomous data measures were used, we have expressed the results in the control and intervention groups of each study as odds ratios (ORs) with 95% confidence intervals (CIs). Three trials (Demetrio et al., 2011; He et al., 2004; Mokhber et al., 2011) had outcome measures as continuous data, these were converted to ORs using R program 'compute.es' (https://cran.r-project.org/web/packages/compute.es/compute.es.pdf) (Del Re, 2010).

In trials that reported both minor and major depression as outcomes, we used data only for major depression for the meta-analysis. Some studies reported open label extensions at the end of double blind follow up period, we report the outcomes at the end of double blind follow up period only. In one study (Su et al., 2014), two different forms of Omega-3 polyunsaturated fatty acids were compared with placebo; the two intervention groups were combined in the meta-analysis.

The number needed to treat (NNT) was calculated to estimate the number of people who would have to receive the pharmacological intervention for one new case of depression to be prevented. The number needed to treat was calculated as the inverse of the absolute risk reduction.

**Data Synthesis and Analysis**

For all meta-analyses, effect estimates (i.e. log odds ratios) and their standard errors were pooled using a random-effects meta-analysis model using restricted maximum likelihood (REML) estimation to produce a summary effect estimate for the mean (or average) effect across studies. A random-effects model was chosen to account for the anticipated variation in trials in different geographical locations, variation in the co-morbid physical conditions and types of pharmacological interventions. The Knapp-Hartung correction was applied when deriving 95% confidence intervals for each summary effect, to account for the uncertainty of the estimate of between-study heterogeneity ($\tau^2$). Forest plots were generated to display the study specific treatment effect estimates with their confidence intervals and the pooled results.

All analyses were conducted using R, with the package 'Metafor' (Viechtbauer, 2010).

**Subgroup analysis and investigation of heterogeneity**

In addition to the primary analysis estimating the efficacy of all pharmacological agents in preventing the onset of depression, we performed a subgroup analysis for the primary outcome to evaluate the evidence for study populations taking different types of antidepressants. We conducted a further subgroup analysis comparing study populations with

different conditions, e.g. post-stroke depression, or postnatal depression. We also performed a meta-regression to adjust for the length of trial follow-up (in weeks).

Heterogeneity is summarised using the $I^2$ statistic and the estimated between-study variance ($\tau^2$) is obtained using REML estimation. To reveal the impact of heterogeneity more clearly, approximate 95% prediction intervals (PI) are also estimated for the treatment effect in any individual study using the formula suggested by Higgins et al. (2009).

**Sensitivity analysis**

We conducted a sensitivity analysis for the primary outcomes to consider whether the review conclusions would have differed if eligibility was restricted to trials without high or unclear risk of bias.

## RESULTS

### Characteristics of included studies

The literature searches from databases and additional resources identified 2890 relevant titles. After screening these records and removing duplicates in accordance with the PRISMA statement, we decided to examine 74 studies in full text. Finally, 30 trials were considered suitable for inclusion. One study (Bronowicki et al., 2010) was only available as a conference abstract and authors did not reply to request for the required data, therefore this study was excluded. In one trial (Narushima et al., 2002), patients only had minor depression and no case of major depressive disorder was reported at the end of follow up period. Therefore, outcome data for incidence of depression from this trial is not included in meta-analysis. The meta-analysis described below is based on 28 studies. The flow diagram with the litearure search results and reasons for excluding studies is shown in figure 1.

**(Fig1 about here)**

The total sample size in these studies was 2745 (control=1347, intervention=1398). With the exception of four articles on preventing postnatal depression, all studies focussed on high-risk populations in different physical conditions. These included studies that aimed at preventing depression associated with interferon treatment in Hepatitis-C (8/28) and post-stroke depression (7/28). Other papers investigated the prevention of depression associated with following conditions: depression following head and neck cancer (2/28), traumatic brain injury (2/28), depression associated with menopause (2/28), acute coronary syndrome (2/28) and malignant melanoma and HIV (1/28). One study on acute coronary syndrome used melatonin (Madsen et al., 2019).

**(Table 1 about here)**

**The efficacy of pharmacological interventions in preventing depression**

The forest plots (fig 2, 3, 5) show the trial-specific and summary odd ratios and 95% CIs (Confidence Intervals) for all trials, for each medical condition and for each antidepressant type. The pharmacological interventions were significantly more effective than the placebo or treatment as usual in preventing the onset of a depressive episode with a pooled OR of OR 0.37 (95% CI: 0.25-0.54)

**(Fig 2 about here)**

The trials that used only antidepressants (22 trials, participants=1958,) had a pooled OR of 0.29 (95% CI: 0.18, 0.46). The overall effect size for Selective Serotonin Reuptake Inhibitors (SSRIs) was also significantly better than the placebo in preventing depression with an OR estimate of 0.29 (95% CI: 0.17, 0.50).

**(Fig 3 about here)**

All Post Stroke Depression (PSD) trials used antidepressants, which were statistically significantly better than placebo in preventing post stroke depression (OR=0.16, 95% CI: 0.05, 0.55). Similarly, pharmacological interventions were more effective in preventing the depressive illness associated with Hepatitis C, (OR=0.56, 95% CI: 0.31, 1.02). The pooled estimates for other conditions are as following: head and neck cancer OR 0·30; (95% CI: 0.13, 0.69), postnatal depression OR= 0.59 (95% CI: 0.33, 1.04), traumatic brain injury OR=0·26 (95% CI: 0.08, 0.84) and acute coronary syndrome OR= 0.56 (95% CI: 0.07, 4.51). The pharmacological interventions for preventing depression in the menopause were not statistically significantly associated with prevention of depressive episodes (OR=0.48, 95% CI: 0.09, 2.49) and in the malignant melanoma the summary OR estimate was 0.09 (95% CI: 0.02, 0.50) (figure 2)

The details of the quality assessment using the Cochrane risk of bias tool are shown in figure 4. Sixteen studies were classified as having low risk of bias. All studies with low risk of bias used antidepressants with the exception of one article in which Melatonin was used (Madsen et al, 2019). Studies with low risk of bias showed a statistically better effect of pharmacological agents in preventing depression (pooled OR 0.43, 95% CI 0.30,0.60) (Fig 5). No publication bias was detected on the visual inspection of the funnel plot or trim and fill analysis (see appendix 2and 3)

**(Figure about 4 here)**

**(Fig 5 about here)**

The NNT for the preventive effect of all pharmacological intervention was seven. In the analysis limited to studies using antidepressants, the NNT was 6 and in studies with low risk of bias the NNT was 8.

**The effect of duration of follow up:**

The duration of intervention varied between 8 to 54 weeks (mean 28.75; SD 15.90 weeks). The meta-regression to adjust for the length of trial follow-up showed that the follow up duration did not have significant effect on the overall effect of the pharmacological interventions [OR 0.99 (P= 0.59; 95% CI 0.96, 1.21)].

**Effects of antidepressants on physical health outcomes**

In view of heterogeneity of outcomes as described below and quality of reported data, it was not possible to conduct meta-analysis of this data. We report a summary of these outcomes below.

Five studies (de Knegt et al., 2011; Diez-Quevedo et al., 2011; Klein et al., 2014; Raison et al., 2007; Schaefer et al., 2012) reported the effect of prophylactic antidepressant treatment in response to anti-viral treatments. Four studies found that prophylactic antidepressant treatment did not help to achieve sustained virologic response (de Knegt et al., 2011; Diez-Quevedo et al., 2011; Raison et al., 2007; Schaefer et al., 2012). The use of antidepressant also had no influence on haematological or biochemical parameters or the dosage reduction of either IFN-alpha or ribavirin (de Knegt et al., 2011). Only one study found (Morasco et al., 2007) that the treatment with Paroxetine helped to achieve a statistically significant sustained viral response (SVR) compared with placebo (SVR on Paroxetine 7/14; 50% versus 2/19; 10.5% on placebo, p=0.019).

Four studies (Klein et al., 2014; Morasco et al., 2007, 2010; Musselman et al., 2001) examined the effect of prophylactic antidepressant treatment on the likelihood of completion of the anti-HCV (Hepatitis C Virus) treatment and adherence with Pegylated Interferon alpha (PEG-IFNα) and Ribavirin. Mussleman et al. (2001) found that Paroxetine treatment significantly decreased the likelihood that interferon alpha therapy would have to be discontinued because of severe depression or related neurotoxic effects (5% in paroxetine as compared to 35% in placebo; relative risk, 0.14 [95% CI 0.05 to 0.85]). However, three studies (Klein et al., 2014; Morasco et al., 2007, 2010) did not find any beneficial effect on adherence with prescribed PEG-IFNα and Ribavirin treatment for HCV or the likelihood of completing the recommended course of treatment for HCV.

Two studies (Almeida et al., 2006; Robinson et al., 2008) found no beneficial effect of prophylactic antidepressants used in PSD on functioning, on cognitive and disability

outcomes or mortality or the duration of hospital stay. Only Zhang et al. (2013) found that the use of Duloxetine was associated with improvement in Mini Mental State Examination (MMSE) scores and activities of daily living. Jorge et al. (2016) reported no beneficial effect of prophylactic Sertraline on a range of cognitive measures including attention, working memory, episodic memory and speed of information processing in patients with traumatic brain injury

**Discussion**

To our knowledge, this is the first systematic review providing a pooled estimate of all pharmacological interventions that have been used for prevention of depression. Majority of pharmacological interventions were used in physical conditions associated with high risk of depression and had significant effect in preventing depression with a medium effect size of OR 0.37 (CI: 0.25, 0.54). The analysis limited to studies with low risk of bias showed slightly higher effect size. Antidepressants were used for prevention in 22 trials and had significant effect in prevention of depression (OR=0.29; CI: 0.18, 0.46), which suggests that use of antidepressants may be a viable strategy for the prevention of depression in physical disorders that have high risk of depression.

Previous meta-analyses studied the effects of antidepressants in preventing depression in a single high risk condition e.g. post-stroke depression (Salter et al., 2013) and depression associated with Hepatitis C (Al-Omari et al., 2013). These meta-analyses showed that the incidence of depression reduced significantly in post stroke depression (Salter et al., 2013) with prophylactic antidepressants in patients who were free of depression at baseline and in those receiving interferon treatment (Al-Omari et al., 2013) for Hepatitis . The subgroup analysis in the present study for these conditions had broadly similar results. However, comparison of those studies with the results of our present meta-analysis is not appropriate in view of the different outcome measures and methodologies used. Other studies such as Sockol et al. (2013) combined both pharmacological and psychological interventions in the meta-analysis of postnatal depression prevention and cannot be compared with our study.

Our study identified the potential role of antidepressants in preventing the onset of depression in number of high-risk conditions. Other agents reported in the included studies, such as selenium, hormone treatments or Omega-3 fatty acids had little evidence and should not be considered for the future prevention studies.

The antidepressants were effective in preventing depression associated with Hepatitis C treatment and Post stroke depression (PSD), which also had the largest number of trials. According to a recent meta-analysis PSD has a cumulative incidence of up to 52% within 5 years of stroke (Ayerbe et al., 2013) and is associated with increased mortality and morbidity (Bartoli et al., 2013). A study based on the Danish Stroke Registry found that the early antidepressant treatment was associated with substantially lower all-cause mortality (Mortensen et al., 2015). Chollet et al. (2011) showed that early prescription of fluoxetine

with physiotherapy enhanced motor recovery after 3 months in patients with ischaemic stroke and moderate to severe motor deficit, although a recent trial did not find the beneficial effect of Fluoxetine in improving functional outcomes after acute stroke(FOCUS Trial Collaboration, 2019). Similarly, a recent study showed that a follow-up depression diagnosis at any time following Coronary Artery Disease (CAD) was found to be associated with a 2-fold higher risk of death than in patients in whom depression is not diagnosed. Depression more strongly predicted death than any other baseline characteristic, risk factor, comorbidity, severity of CAD, and follow-up events (May et al., 2017). The high burden of disease caused by cardiovascular disease, the potential benefits in preventing depression in these disorders and practical problems in identification and diagnosis of depression following CVA (Cardio Vascular Accident) imply that depression associated with cardiovascular disorders may be a feasible target for prevention in future studies.

Two previous meta-analyses found that preventative psychological interventions lowered the incidence of depression by about 21% compared with controls (Cuijpers et al., 2008; van Zoonen et al., 2014). This was considered to be clinically relevant effect size. These systematic reviews, however, included a wide range of psychological interventions including cognitive behaviour therapy (CBT), interpersonal therapy and problem solving therapy. Considering that antidepressants are relatively low cost and easy to use in clinical practice, the evidence for the effectiveness of antidepressants may be relatively easy to translate into public health interventions. A combination of the psychotherapy and antidepressants may be more effective in prevention of depression, as is the case in treatment of depression. This should be explored in future studies.

Depression is predicted to rank first for global disease burden, in high-income countries by 2030 (Mathers & Loncar, 2006) and the prevention must be a global priority (Cuijpers et al., 2012). The most effective way of preventing depression was also identified as the top most priority by patients, carers, medical professionals and academics in a recent study by The James Lind Alliance Priority Setting Alliance (James Lind Alliance, 2016) .The prophylactic treatments in high-risk populations associated with physical comorbidity can prove a useful strategy for preventing depression and high morbidity associated with these disorders.

The Numbers Needed to Treat (NNT) for the pharmacological interventions in order to prevent one additional was seven. The use of NNT in this population where the base rate for depression can vary between different conditions is problematic (Stang et al., 2010). However, this helps to put the finding in a perspective. The NNT for Warfarin in preventing an ischaemic stroke in patients with atrial fibrillation is 25 (Aguilar & Hart, 2005). The NNT to prevent one myocardial infarction over 5 years of aspirin use is 118 (US Preventive Services Task Force, 2009). The preventive studies using pharmacological interventions in Psychiatry are rare. One systematic review (Sijbrandij et al., 2015) that examined the pharmacological interventions to prevent trauma related psychiatric disorders based on meta-

analysis of both RCTs and cohort studies, found NNT of 11 but the effect was non-significant when only RCTs were included in the sub analysis.

Future research needs to examine the acceptability of antidepressant use by service users to prevent rather than treat the depression before the strategy can be considered for routine clinical practice. All studies used antidepressants in therapeutic doses. It is possible that the dose required for preventing depression is lower than the therapeutic doses, thus further improving the acceptability and tolerability of the antidepressants in prevention of the disorder. Studies testing different doses, with longer follow up periods and adequate reporting of safety and the other relevant outcomes such as disability and quality of life are needed.

**Limitations**: We used a comprehensive search strategy and it is unlikely that any published studies were missed. The robust quality criteria to determine the risk of bias including the use of validated measures to exclude depression at the baseline and relatively low heterogeneity are strengths of the present study. We used a broad search criterion to identify all studies that aimed to prevent depression. However, the evidence for prevention is limited to use of pharmacological interventions only in high risk conditions.

The main limitation of the review is the quality of the primary evidence. The statistical heterogeneity was low but the included papers were clinically heterogeneous in terms of participants, underlying physical conditions and duration of follow-up. The total sample size in some conditions was small, e.g. four trials had 218 participants testing three different interventions in Postnatal depression. The short follow up period of about 28 weeks is a major limitation in determining the long term effect of preventive treatments. It is also not clear whether the pharmacological interventions reduced the incidence of depression or only delayed onset. However, both preventing and delaying onset are important from a clinical and public health perspective.

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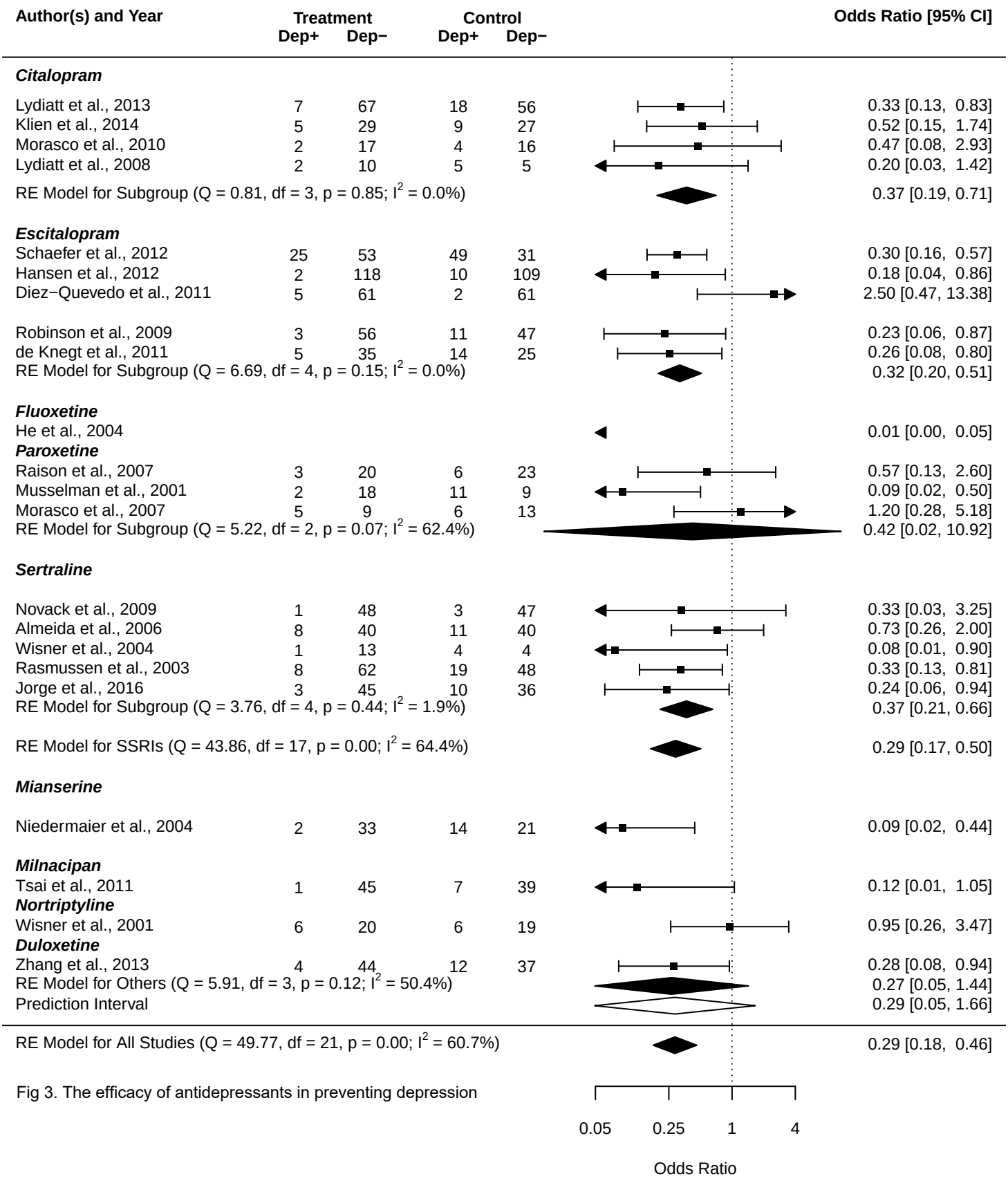
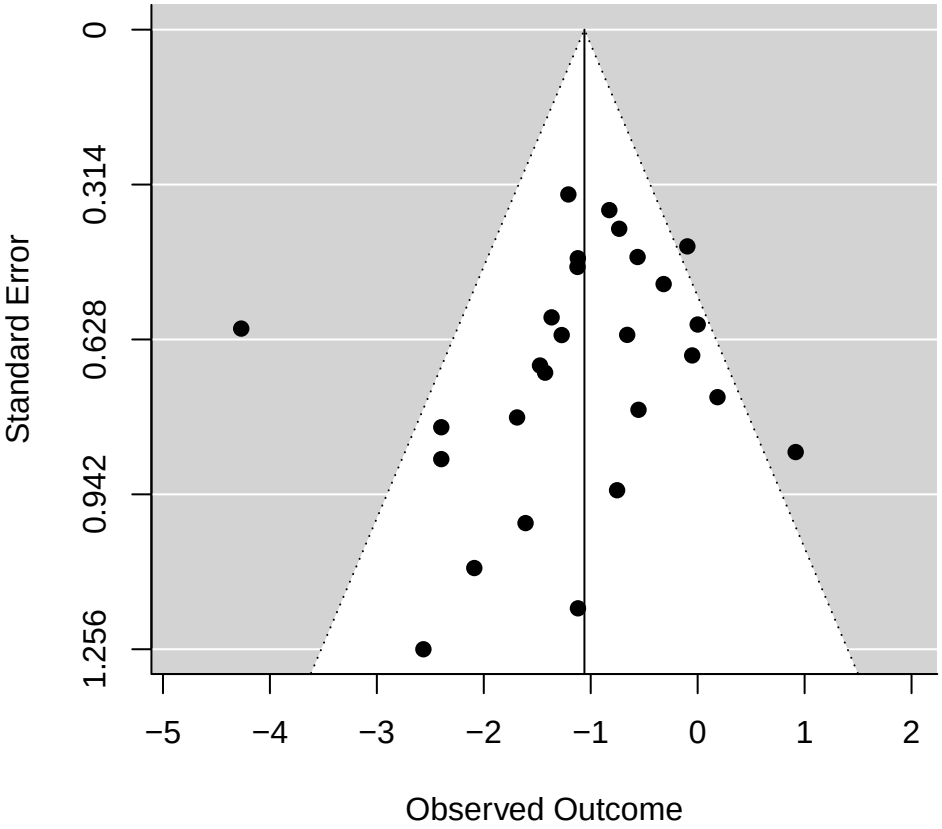



Fig 3. The efficacy of antidepressants in preventing depression

PHARMACOLOGICAL INTERVENTIONS FOR PREVENTION OF DEPRESSION: FUNNEL PLOT WITH TRIM AND FILL



# PRISMA 2009 Checklist for the article:

Appendix 1. **Pharmacological interventions for prevention of depression: systematic review and meta-analysis.**

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | 1 |
| **ABSTRACT** | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 1 |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 2 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 2 |
| **METHODS** | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | 4 |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 3,4 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 3,4 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | 3,4 |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 4 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 4 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 5 |

# PRISMA 2009 Checklist for the article:

Appendix 1. **Pharmacological interventions for prevention of depression: systematic review and meta-analysis.**

| | | | |
|---|---|---|---|
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 4,5 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | 4 |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis. | 5 |



| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 4 |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | 6 |
| **RESULTS** | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 6 and figure 1 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | 6 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | 7 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | 6-8 |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | 6-8 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | 7 |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | 7 |
| **DISCUSSION** | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 8-9 |

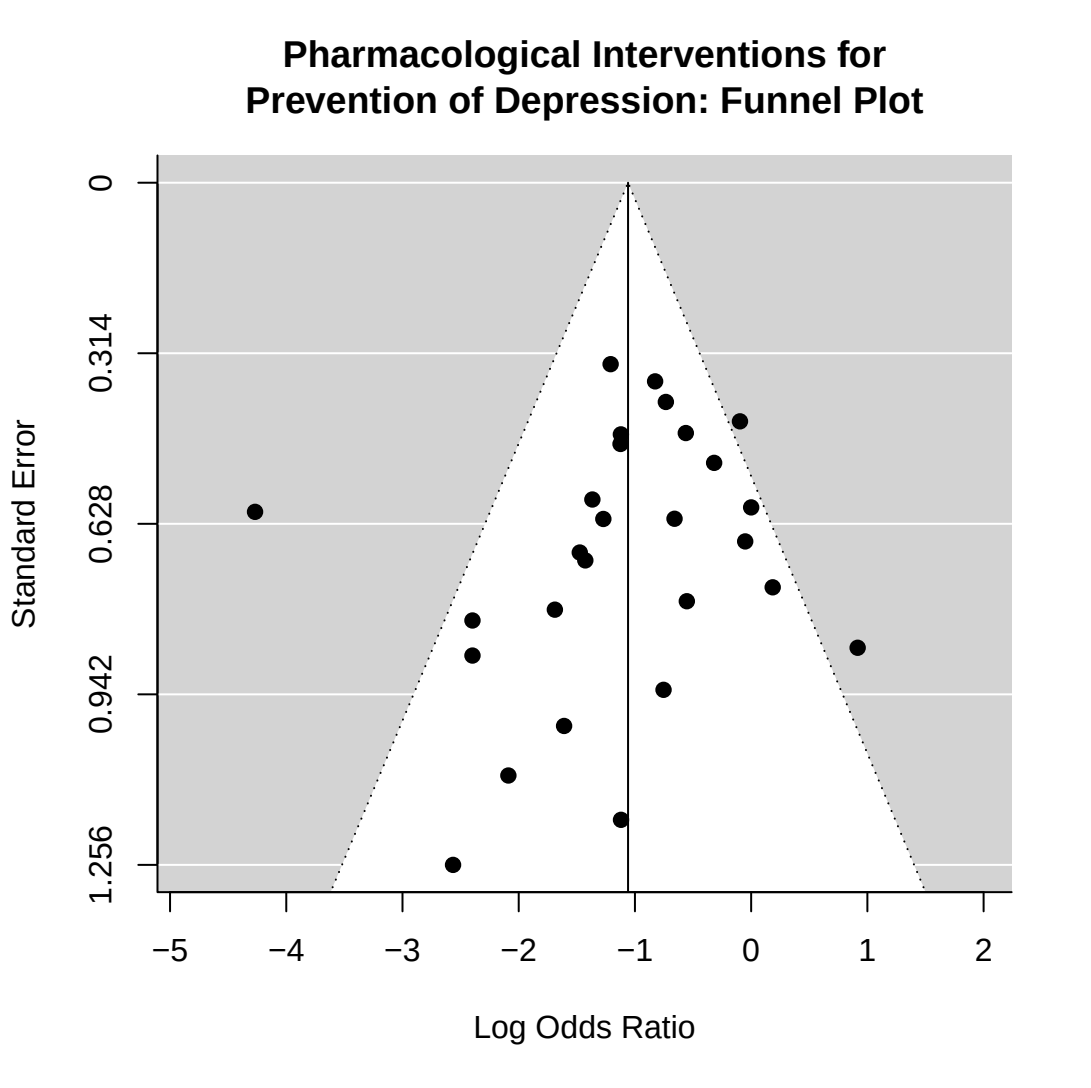
# PRISMA 2009 Checklist for the article:

Appendix 1. **Pharmacological interventions for prevention of depression: systematic review and meta-analysis.**

| | | | |
|---|---|---|---|
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 10 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 8-10 |
| **FUNDING** | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 10 |

*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(6): e1000097. doi:10.1371/journal.pmed1000097

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


Pharmacological Interventions for
Prevention of Depression: Funnel Plot
Standard Error
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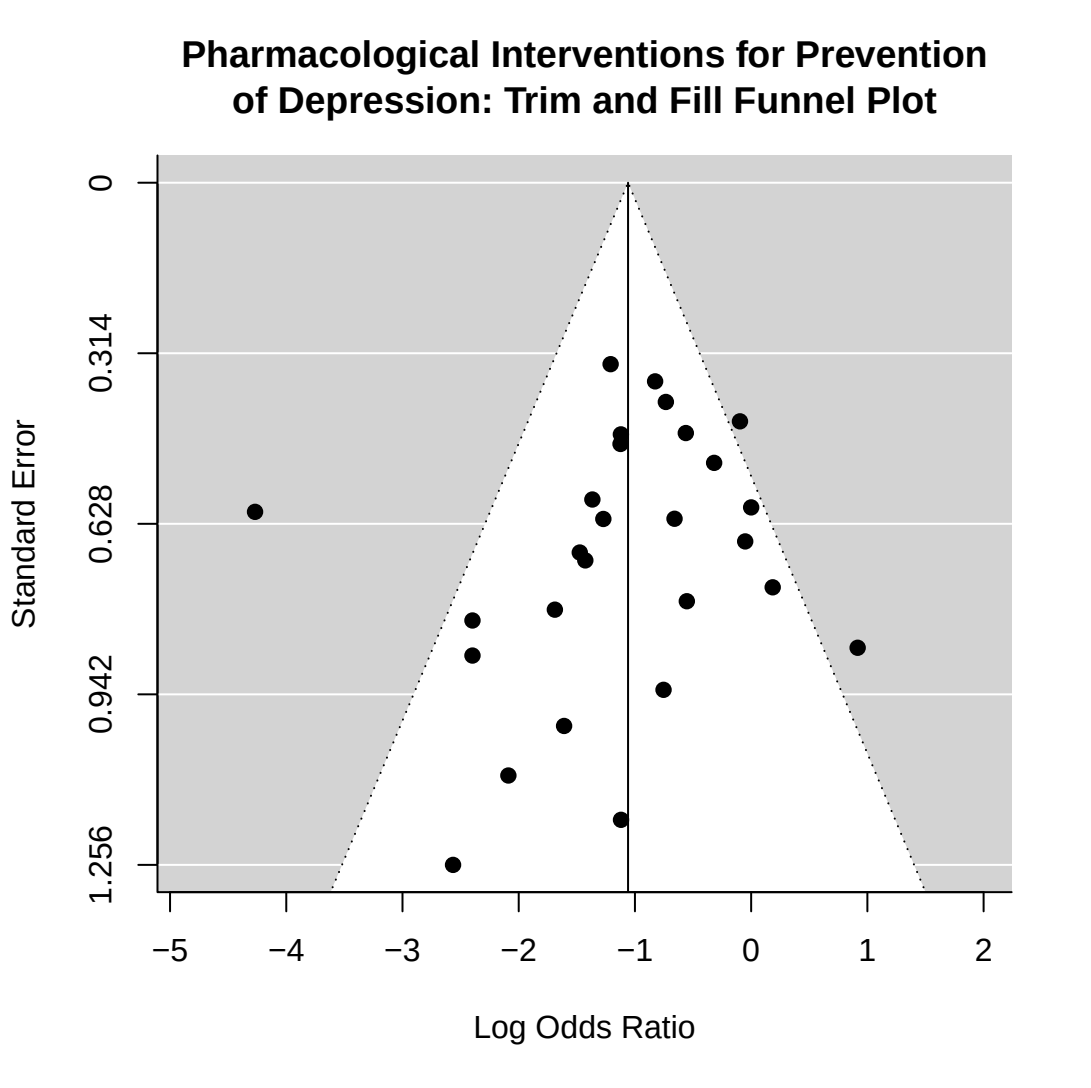
Pharmacological Interventions for Prevention of Depression: Trim and Fill Funnel Plot
Standard Error
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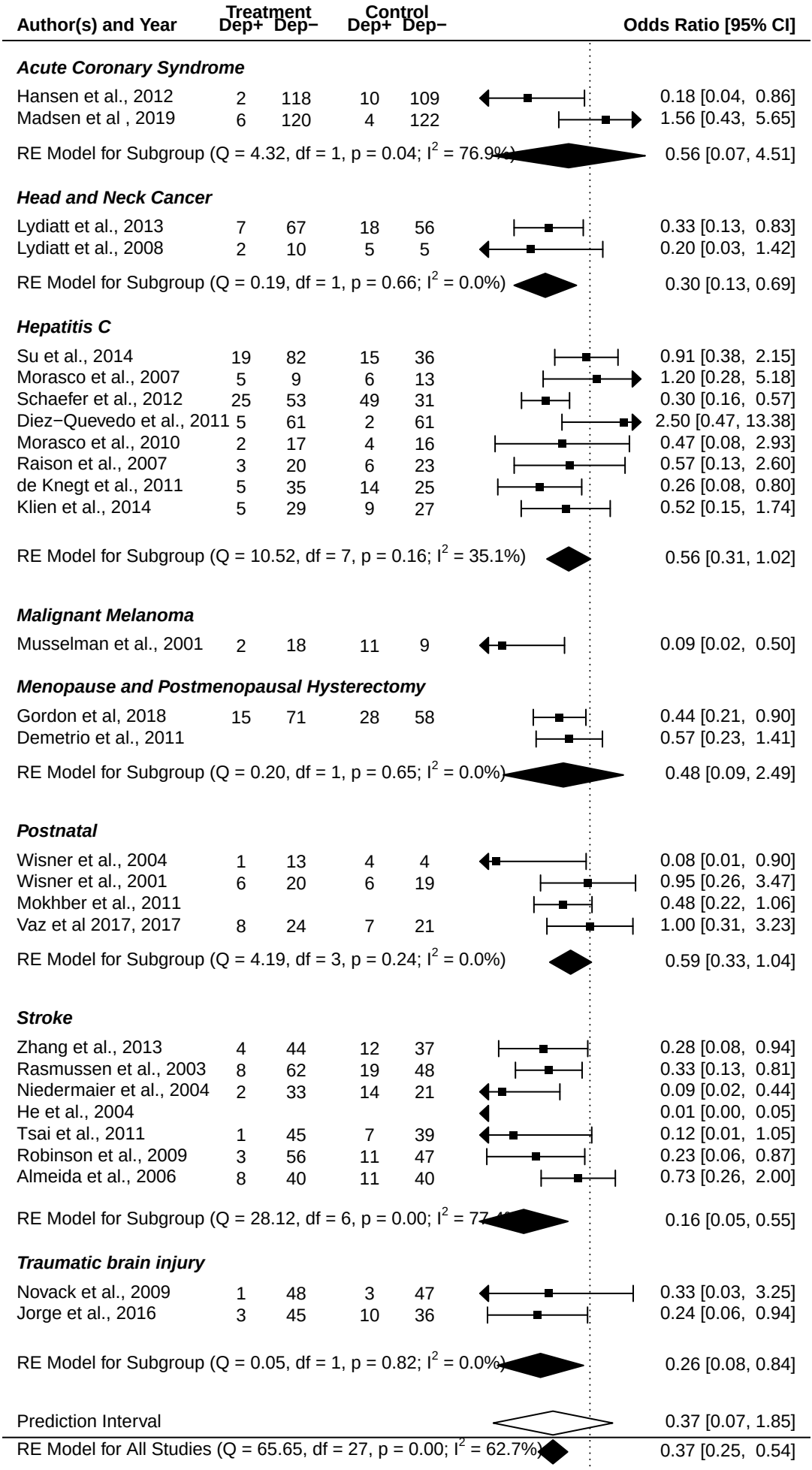
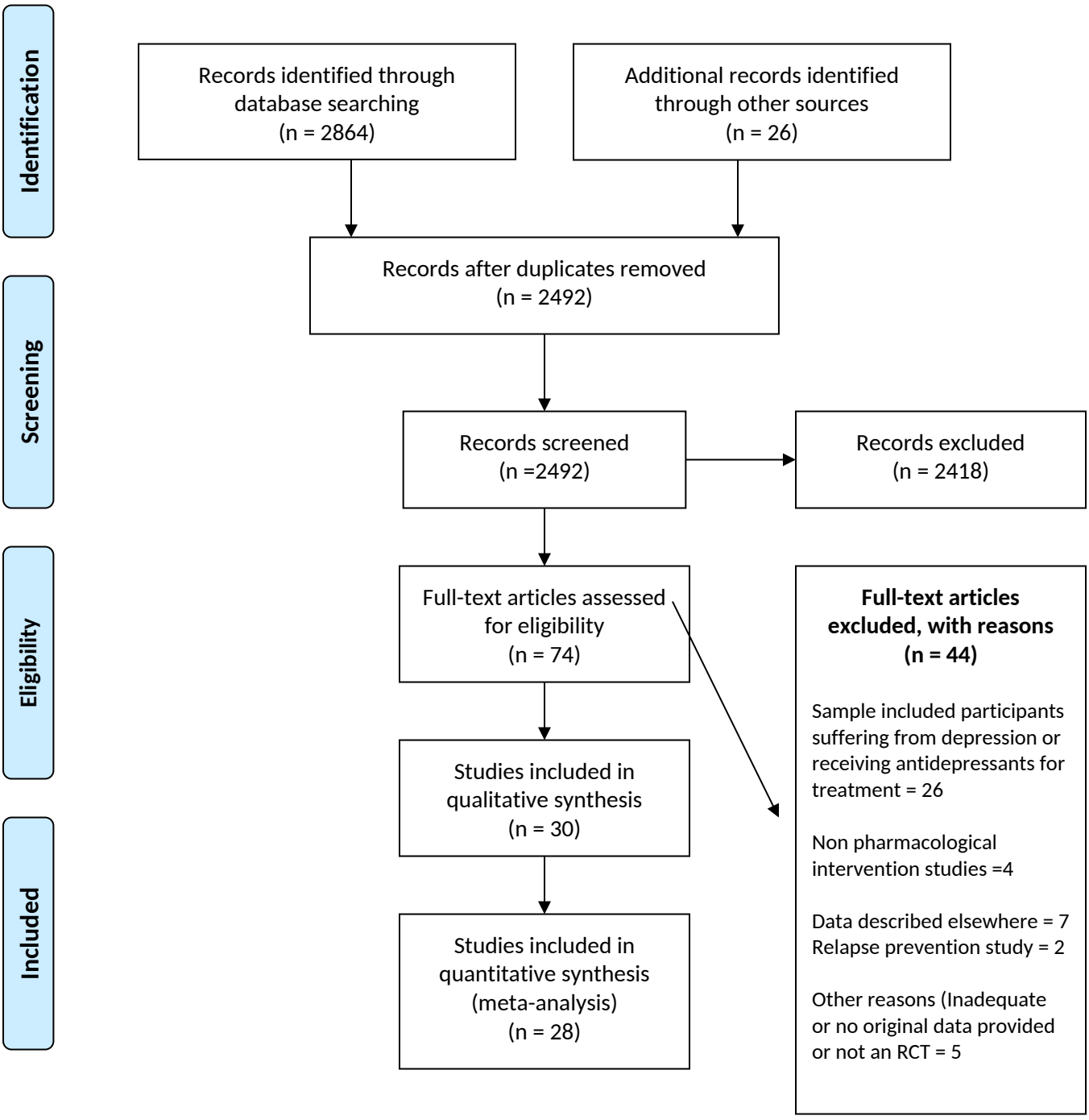



Fig 2. Overall efficacy of all pharmacological interventions and efficacy in different physical conditions

**Fig: 1: PRISMA Flow Diagram Pharmacological Interventions For Prevention Of Depression**



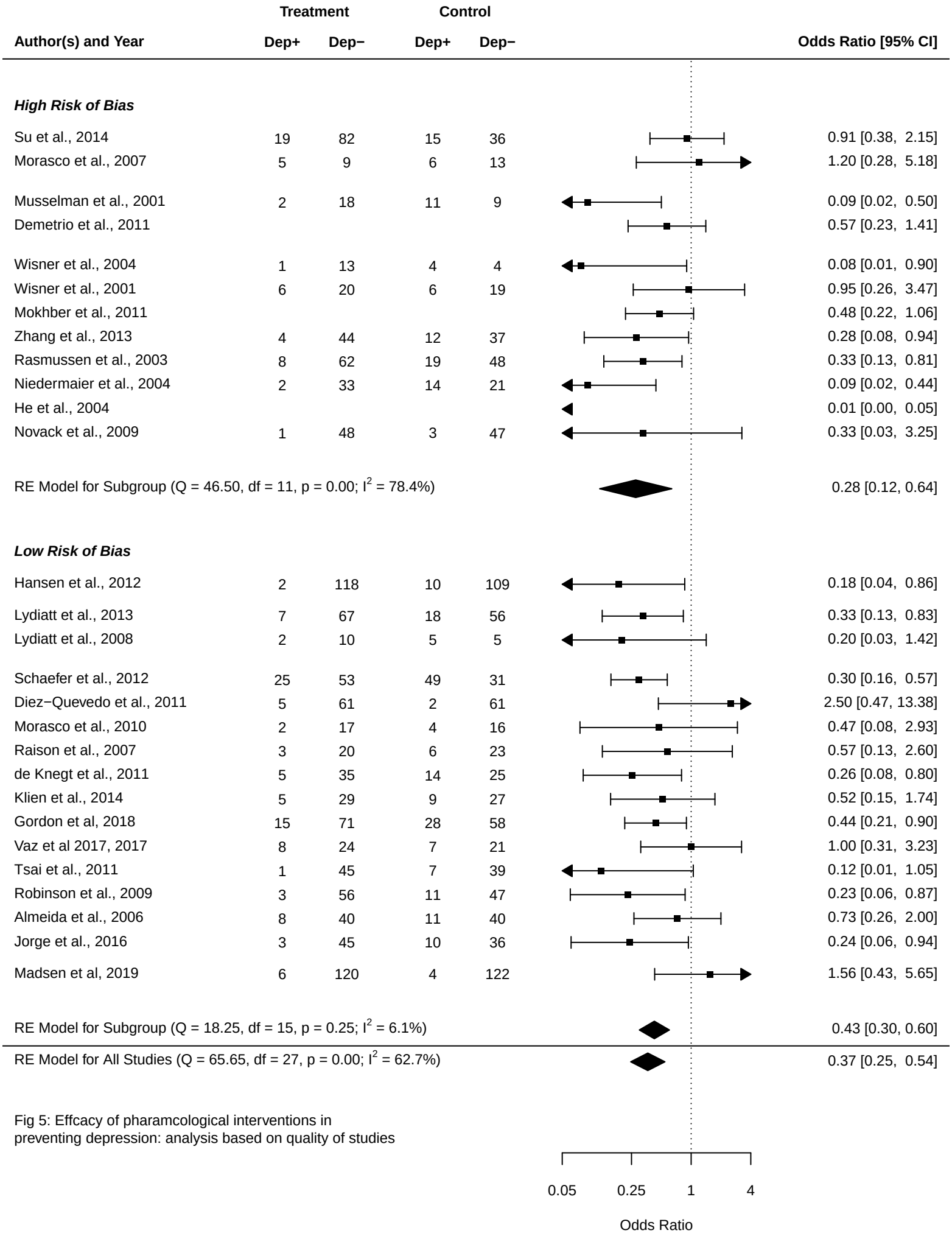



Fig 5: Effcacy of pharamcological interventions in preventing depression: analysis based on quality of studies

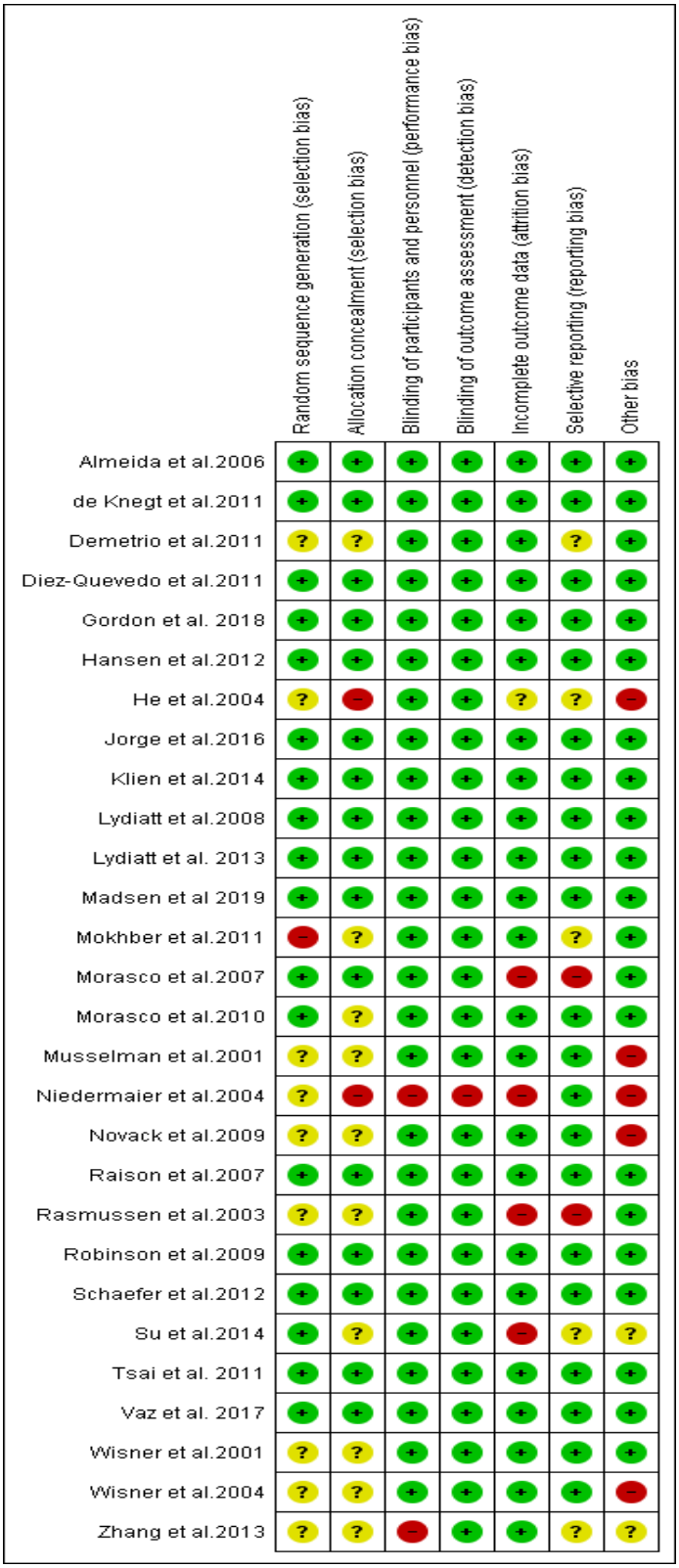



Figure 4 Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

**Table 1: Characteristics of included studies**

| Authors | Year | Target population | Control (n) | Intervention (n) | Total (n) | Instrument used for diagnosis* | Pharmacological Interventions | Follow-up (weeks) |
|---|---|---|---|---|---|---|---|---|
| Almeida et al . | 2006 | Stroke | 51 | 48 | 99 | HADS (Zigmond and Snaith, 1983) | Sertraline | 24 |
| de Knegt et al . | 2011 | Hepatitis C | 39 | 40 | 79 | MINI (Sheehan et al., 1998) | Escitalopram | 48 |
| Demetrio et al | 2011 | Postmenopausal Hysterectomy | 36 | 30 | 66 | BDI (Beck et al., 1961) | CEE* | 26 |
| Diez-Quevedo et al. | 2011 | Hepatitis C | 63 | 66 | 129 | SCID-DSM-IV (First et al., 1994) | Escitalopram | 12 |
| Gordon et al | 2018 | Postmenopausal Hysterectomy | 86 | 86 | 172 | CES-D*,(Radloff, 1977) | Transdermal estradiol | 52 |
| Hansen et al. | 2012 | Acute coronary syndrome | 119 | 120 | 239 | SCAN (Wing et al., 1990) | Escitalopram | 52 |
| He et al | 2004 | Stroke | 35 | 36 | 71 | HAM-D (Hamilton, 1960) | Fluoxetine | 8 |
| Jorge et al. | 2016 | Traumatic brain injury | 46 | 48 | 94 | DSM-IV(American Psychiatric Association, 1994) | Sertraline | 24 |
| Lydiatt et al. | 2008 | Head and Neck Cancer | 10 | 12 | 22 | HRSD(Hamilton, 1960) | Citalopram | 12 |
| Lydiatt et al | 2013 | Head and Neck Cancer | 74 | 74 | 148 | QIDS-SR (Trivedi et al., 2004) | Escitalopram | 16 |
| Klein et al. | 2014 | Hepatitis C | 36 | 34 | 70 | BDI(Beck et al., 1961) | Citalopram | 48 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Madsen et al | 2019 | Acute coronary syndrome | 126 | 126 | 252 | MDI | Melatonin | 12 |
| Mokhber et al | 2011 | Postnatal | 41 | 44 | 85 | EPDS (Cox et al., 1987) | Selenium | 26 |
| Morasco et al. | 2010 | Hepatitis C | 20 | 19 | 39 | DSM- SCID(First et al., 1994) | Citalopram | 26 |
| Morasco et al. | 2007 | Hepatitis C | 19 | 14 | 33 | DSM-SCID(First et al., 1994) | Paroxetine | 26 |
| Musselman et al. | 2001 | Malignant Melanoma | 20 | 20 | 40 | DSM-IV(American Psychiatric Association, 1994) | Paroxetine | 14 |
| Niedermaier et al. | 2004 | Stroke | 35 | 35 | 70 | DSM-IV(American Psychiatric Association, 1994) | Mianserine | 51 |
| Novack et al. | 2009 | Traumatic brain injury | 50 | 49 | 99 | HDRS (Hamilton, 1960)+ SCID(First et al., 1994) | Sertraline | 13 |
| Raison et al | 2007 | Hepatitis C | 29 | 23 | 52 | DSM-SCID(First et al., 1994) | Paroxetine | 26 |
| Rasmussen et al. | 2003 | Stroke | 67 | 70 | 137 | HAM-D(Hamilton, 1960) | Sertraline | 54 |
| Robinson et al. | 2009 | Stroke | 58 | 59 | 117 | DSM-SCID(First et al., 1994) | Escitalopram | 54 |
| Schaefer et al. | 2012 | Hepatitis C | 80 | 78 | 158 | MADRS(Montgomery and Asberg, 1979) | Escitalopram | 38 |
| Su et al. | 2014 | Hepatitis C | 51 | 51 | 102 | MINI(Sheehan et al., 1998) | DHA* | 24 |
| | | | | 50 | 50 | MINI(Sheehan et al., 1998) | EPA* | 24 |
| Tsai et al. | 2011 | Stroke | 46 | 46 | 92 | DSM-IV(American Psychiatric Association, 1994) | Milnacipan | 54 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Vaz et al | 2017 | Postnatal | 28 | 32 | 60 | EPDS(Cox et al., 1987) | EPA & DHA (Fish oil Supplement ) | 12 |
| Wisner et al. | 2001 | Postnatal | 25 | 26 | 51 | HAM-D (Hamilton, 1960)& RDC(Spitzer et al., 1978) | Nortryptaline | 20 |
| Wisner et al. | 2004 | Postnatal | 8 | 14 | 22 | HAM-D (Hamilton, 1960) | Sertraline | 17 |
| Zhang et al. | 2013 | Stroke | 49 | 48 | 97 | HAM-D (Hamilton, 1960) | Duloxetine | 12 |

* BDI: Beck Depression Inventory, CES-D: Center for Epidemiological Studies–Depression Scale, DSM: Diagnostic and Statistical Manual of Mental Disorders, SCID: Structured Clinical Interview for DSM, EPDS: Edinburgh Postnatal Depression Scale, HADS: Hospital Anxiety and Depression Scale, HAM-D: Hamilton Rating Scale for Depression, MADRS: Montgomery–Åsberg Depression Rating Scale, MINI: Mini-international neuropsychiatric interview, SCAN: Schedule for Clinical Assessment in Neuropsychiatry; QIDS-SR: Quick Inventory of Depressive Symptomatology-Self-Report, RDC: Research Diagnostic Criteria. CEE: Conjugated Equine Estrogens, DHA: Docosahexaenoic acid, EPA: Eicosapentaenoic acid, MDI: Major Depression Inventory

**Conflict of Interest Statement**

All authors have no conflict of interest to declare in relation to this manuscript

## Author statement

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## Contributor statement

**SF** conceived the idea and wrote the protocol. He was involved in literature search, identification of relevant studies, data extraction and wrote the first draft.
**SPS** advised on the protocol. He was involved in discussion on selection of articles, data-extraction, feedback on data entry, initial data-analyses, and management of database.
**DB** developed the analysis plan and supervised the analysis.
**FN** was involved in identification of suitable studies, extracting the data and analysis.
**MA** was involved the identification of studies, final selection of studies and analysis of the data.
All authors contributed to writing the final draft.

**PHARMACOLOGICAL INTERVENTIONS FOR PREVENTION OF DEPRESSION IN HIGH RISK CONDITIONS: SYSTEMATIC REVIEW AND META-ANALYSIS.**


## ABSTRACT

**Background:** Depressive disorders account for almost half of all Disability Adjusted Life Years caused by psychiatric disorders but efficacy of pharmacological intervention to prevent depressive disorders is not known. We aimed to assess efficacy of pharmacological treatments in prevention of depression.

**Methods:** We searched PubMed**,** Psych Info, EMBASE, and CINHAL from 1980 to April 2018 and bibliographies of relevant systematic reviews. We selected randomised controlled trials (RCTs) that used a pharmacological intervention to prevent the onset of the new depressive episode in adult population. Study selection, data extraction and reporting is done following PRISMA guidelines. Data were pooled using random-effects meta-analysis.

Results: 28 trials (2745 participants) ~~27 trials (2493 participants)~~ were included in meta-analysis. Antidepressants (22 studies), Selenium, Hormone Replacement Therapy ~~and~~ Omega-3 fatty acids and Melatonin ~~-~~were used to prevent depression, mostly in physical conditions associated with high risk of depression All pharmacological interventions [pooled Odds Ratios (OR) 0.37 CI (0.25-0.54)] , and antidepressants (OR 0.29, 95% CI: 0.18~~7~~, 0.46~~50~~) were significantly more effective than placebo in preventing depression. Antidepressants were significantly better than placebo in trials that had low risk of bias (n=16; 0.43 [0.30, 0.60]) , in preventing post stroke depression (OR=0.16, 95% CI: 0.~~·~~05, 0.~~·~~55) and depression associated with Hepatitis C (OR=0.51, 95% CI: 0.31, 1.02).~~·~~

~~All pharmacological interventions [pooled Odds Ratios (OR) 0.35,; 95% CI: 0.23, 0.50] and antidepressants (OR 0.29,; 95% CI: 0.17, 0.50) were significantly more effective than placebo in preventing depression. Antidepressants were significantly better than placebo in trials that had low risk of bias (n=15; OR 0.35,; CI: 0.23, 0.52), in preventing post stroke depression (OR=0.16, 95% CI: 0·05, 0·55) and depression associated with Hepatitis C (OR=0.51, 95% CI: 0.31, 1.02)~~.

**Limitations** include small number of studies focussed only on high risk conditions and short follow up in most studies.

**Conclusions:** Prevention of depression may be possible in patients who have high-risk conditions such as stroke but the strategy requires complete risk and benefits analysis before it can be considered for clinical practice



**Key Words:** Depression, depressive illness, prevention, drugs, pharmacological agents, meta-analysis

## INTRODUCTION

The global burden of diseases study estimated that depressive disorders account for 40% of the Disability Adjusted Life Years (DALYS) caused by all mental and substance abuse disorders (Whiteford et al., 2013). It is estimated that even if the coverage, clinical competence and compliance become optimal with no major barriers to health service delivery and financing, only 36% of the total burden of disease caused by depressive disorders could be averted using current interventions and knowledge (Andrews et al., 2004). This situation demands that the prevention of depressive illness be a major health priority (Cuijpers et al., 2012).

Three types of preventive approaches have been used in prevention of depression(van Zoonen et al., 2014). The universal prevention focuses on the whole population group regardless of risk status(Spence et al., 2003). Selective prevention targets individuals who are at higher risk of developing a condition such as women during the postnatal period. Indicated prevention targets the individuals who are identified through biological markers to mental disorders, but who do not yet meet the diagnostic criteria for depressive illness(Muñoz et al., 2010). The pharmacological interventions for prevention of depression have mainly used the selective approach. These include focussing on the high risk groups such as those who are at higher risk to develop depression following physical conditions like hepatitis C, stroke or acute coronary syndrome (see below). This approach has the advantage that population at risk is already receiving medical care and thus relatively easy to identify and target.

**Commented [1]:** Kim van Zoonen, Claudia Buntrock, David Daniel Ebert, Filip Smit, Charles F Reynolds, III, Aartjan TF Beekman, Pim Cuijpers, Preventing the onset of major depressive disorder: A meta-analytic review of psychological interventions, *International Journal of Epidemiology*, Volume 43, Issue 2, April 2014, Pages 318–329, https://doi.org/10.1093/ije/dyt175

**Commented [2R2]:**

**Commented [3]:** Spence SH, Sheffield JK, Donovan CL. Preventing adolescent depression: An evaluation of the problem solving for life program, J Consult Clin Psychol, 2003, vol. 71 (pg. 3-13)

**Commented [4]:** Munoz RF, Cuijpers P, Smit F, Barrera AZ, Leykin Y, Prevention of Major Depression. *Annu Rev Clin Psychol,* 2010, vol. 6, 181-212.

The pharmacological treatment that can prevent the onset of depressive disorders would represent a major public health advance in averting the colossal burden caused by the illness, as the currently available pharmacological treatments are relatively cheap, are available universally and can be easily administered (Kupfer, 2005). The systematic reviews of the preventive strategies in depression have mainly focused on psychological interventions (Cuijpers et al., 2008). The pharmacological interventions for the prevention of depression have been systematically reviewed for specific categories such as Post-Natal Depression (Miller et al., 2013; Molyneaux et al., 2018). No systematic review and meta-analysis of all the pharmacological interventions used for prevention of depression is published.

We aim to identify and evaluate the efficacy of all pharmacological treatments that have been used for preventing the onset of depressive illness in adult populations.

## METHODS

### Outcome measures:

The primary outcome of interest for this review is the incidence of depressive disorders in the intervention group compared with the control group post-intervention and at follow-up. We used the incidence based on the diagnostic instrument that was specified as primary diagnostic instrument, as mentioned in the description of primary end point of each study. Where this was not clear, we preferred the interview based diagnosis over the diagnosis based on cut-off point of a scale.

Since majority of included trials were in patients with persisting physical conditions, we also report the effects of interventions on physical health outcomes, such as disability or the effect of prophylactic antidepressant treatment in response to anti-viral treatments.

**Data Sources and Searches**

The meta analysis was done and is reported following ed the PRISMA guidelines for identification and selection of studies, data extraction and reporting (see the online appendix-1 for the PRISMA 2009 Checklist for reporting the article).

The search was performed in the electronic data bases PubMed, PsychInfo, EMBASE, and CINHAL, with the last updated search in Januaryb2020. September, 2018. The search was limited to randomised controlled trials (RCT) published from 1980, since clinical trials based on diagnostic criteria relevant to this review did not exist before that time. Searches were conducted using the following search strings using both MeSH terms and text words: "depression" OR "antidepressants" OR "prevention" OR "preventing onset of depression" OR "preventing depressive episode(s)" OR "preventing depressive" OR "prevention" OR "prophylaxis"; . "depression" AND "antidepressants" AND ("prevention" OR "preventing onset of depression" OR "preventing depressive episode(s)" OR "preventing depressive" OR "prophylaxis").. Following strings were applied to eliminate the articles related to preventing the relapse of depressive disorders: "maintenance therapy" OR "recurrent" OR "recurrence" OR "relapsed" OR "relapsing" OR "pre-existing" OR "pre-existing depression". We identified 15 potentially relevant systematic reviews (appendix-21) on prevention of depression, and hand searched their bibliographies for additional references.

**Study Selection**

We included studies with the following characteristic:

1. Published RCTs that included participants aged 18 years and above who were not suffering from depressive illness or not taking any treatment for depression at the start of the trial.
2. A pharmacological intervention initiated at least in one arm of the trial with the aim of preventing the onset of the new depressive episode.
3. Studies reported at least one outcome measure related to the prevention of depression.

We adopted the definition of prevention as recommended by the Institute of Medicine Report (National Research Council (US) and Institute of Medicine (US) Committee on the Prevention of Mental Disorders and Substance Abuse Among Children, Youth, and Young Adults: Research Advances and Promising Interventions, 2009). Primary prevention would include interventions aimed at reducing the incident cases only. We included studies that recruited participants with a previous

history of depression, but who were not suffering from depression at the beginning of the trial. The onset of depressive illness was defined using standard diagnostic criteria, such as International Classification of Disease (ICD-10), or the Diagnostic and Statistical Manual (DSM), based on standardised clinical interview or using score above cut off point on a standardised and valid rating scales.

The relapse prevention studies which evaluated the effectiveness of maintenance treatment to prevent the relapse of depressive illness were excluded. Studies that used herbal preparations were also excluded, as these are usually combination of different chemical entities and it is not possible to identify an active pharmacological agent.

Two reviewers (SF and MA) identified the relevant studies from the titles and abstracts and obtained the potentially relevant full-text articles. Both reviewers read these to decide whether they met the inclusion criteria. A consensus was reached after mutual discussion in case of disagreement.

**Data Extraction and Quality Assessment;**

Project Registration, data management, quality assessment and coordination amongst the author were done using Metabase, a web-based data management tool (https://meta.mediware.pro) developed and managed by MediWare Health Informatics. The authors have used the system for a number of previous meta-analyses (Singh et al., 2010). Metabase allows project-based authorisation and differential access to all necessary tools, including access to the study protocol, full text articles, and data items for project members. All data were entered on pre-specified forms built in Metabase.

Two authors (SF and SPS) extracted the following data items from the selected papers: diagnosis and diagnostic criteria, quality measures, specific details of arms of trials, including sample characteristics and baseline medications, names of intervention, and duration of treatment; data types and format, and names of scales; and pre-trial and post -trial outcome scores. Any disagreement on data extraction was resloved through mutual discussion between the authors who extracted the data.

**Quality assessment of included studies**

We used the Cochrane Collaboration tool for assessing the risk of bias in randomised trials (Higgins et al., 2011) that uses the following seven domains: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective outcome reporting and 'other' bias. These domains are classified as having high, low and unclear risk of bias. In the 'other' bias domain, we considered whether a validated instrument/measurement was used to ascertain that participants were free of depressive illness at the baseline, as the inadequate screening for depression at baseline could result in recruiting participants with depression, which could inflate the effect of the intervention.

The methodological quality of the selected trials was assessed independently by two authors (SF and SS). A study was classified as having low risk of bias if the following items were all categorized as having low risk of bias based on Cochrane Collaboration tool: random sequence generation, blinding of participants and personnel, blinding of outcome assessment and 'other' bias. If any of these items were categorized as high risk or unclear, the study was classified as having high risk of bias.

**Measures of treatment effect.** Where dichotomous data measures were used, we have expressed the results in the control and intervention groups of each study as odds ratios (ORs) with 95% confidence intervals (CIs). Three trials (Demetrio et al., 2011; He et al., 2004; Mokhber et al., 2011)~~(Demetrio et~~

al., 2011; He, Kong, & Xu, 2004; Mokhber et al., 2011) had outcome measures as continuous data, these were converted to ORs using R program 'compute.es' (https://cran.r-project.org/web/packages/compute.es/compute.es.pdf) (Del Re, 2010).

In trials that reported both minor and major depression as outcome, we used data only for major depression for the meta-analysis. Some studies reported open label extensions at the end of double blind follow up period, we report the outcomes at the end of double blind follow up period only. In one study (Su et al., 2014), two different forms of Omega-3 polyunsaturated fatty acids were compared with placebo; the two intervention groups were combined in the meta-analysis.

The number needed to treat (NNT) was calculated to estimate the number of people who would have to receive the pharmacological intervention for one new case of depression to be prevented. The number needed to treat was calculated as the inverse of the absolute risk reduction.

**Data Synthesis and Analysis**

For all meta-analyses, effect estimates (i.e. log odds ratios) and their standard errors were pooled using a random-effects meta-analysis model using restricted maximum likelihood (REML) estimation to produce a summary effect estimate for the mean (or average) effect across studies. A random-effects model was chosen to account for the anticipated variation in trials in different geographical locations, variation in the co-morbid physical conditions and types of pharmacological interventions. The Knapp-Hartung correction was applied when deriving 95% confidence intervals for each summary effect, to account for the uncertainty of the estimate of between-study heterogeneity ($\tau^2$). Forest plots were generated to display the study specific treatment effect estimates with their confidence intervals and the pooled results.

All analyses were conducted using R, with the package 'Metafor' (Viechtbauer, 2010).

**Subgroup analysis and investigation of heterogeneity**

In addition to the primary analysis estimating the efficacy of all pharmacological agents in preventing the onset of depression, we performed a subgroup analysis for the primary outcome to evaluate the evidence for study populations taking different types of antidepressants. We conducted a further subgroup analysis comparing study populations with different conditions, e.g. post-stroke depression, or postnatal depression. We also performed a meta-regression to adjust for the length of trial follow-up (in weeks).

Heterogeneity is summarised using the $I^2$ statistic and the estimated between-study variance ($\tau^2$) is obtained using REML estimation. To reveal the impact of heterogeneity more clearly, approximate 95% prediction intervals (PI) are also estimated for the treatment effect in any individual study using the formula suggested by Higgins et al. (2009).

**Sensitivity analysis**

We conducted a sensitivity analysis for the primary outcomes to consider whether the review conclusions would have differed if eligibility was restricted to trials without high or unclear risk of bias.

**RESULTS**

**Characteristics of included studies**

The literature searches from databases and additional resources identified ~~2505~~ ~~2479~~ 2890 -relevant titles. After screening these records and removing duplicates in accordance with the PRISMA statement, we decided to examine 7~~40~~ studies in full text. Finally, ~~29~~ 30 trials were considered suitable for inclusion. One study (Bronowicki et al., 2010) was only available as a conference abstract and authors did not reply to request for the required data, therefore this study was excluded. In one trial (Narushima, Kosier, & Robinson, 2002), patients only had minor depression and no case of major depressive disorder was reported at the end of follow up period. Therefore, outcome data for incidence of depression from this trial is not included in meta-analysis. The meta-analysis described below is based on 28 studies. The flow diagram with the litearure search results and reasons for excluding studies is shown in figure 1.

**(Fig1 about here)**

The total sample size in these studies was ~~2493~~ 2745 (control=~~1221~~1347, intervention=~~1272~~1398)

. With the exception of four articles on preventing postnatal depression, all studies focussed on high-risk populations in different physical conditions. These included studies that aimed at preventing depression associated with interferon treatment in Hepatitis-C (~~7~~8/2~~7~~8) and post-stroke depression (7/27). Other papers investigated the prevention of depression associated with following conditions:, depression following head and neck cancer (2/2~~7~~8), traumatic brain injury (2/2~~7~~8), depression associated with menopause (2/2~~7~~8), acute coronary syndrome (~~2~~1/2~~7~~8) and malignant melanoma and HIV (1/2~~7~~8). One study on acute coronary syndrome used melatonin (Madsen et al., 2019).

**(Table 1 about here)**

**The efficacy of pharmacological interventions in preventing depression**

The forest plots (fig 2, 3, 5) show the trial-specific and summary odd ratios and 95% CIs (C~~e~~onfidence Intervals) for all trials, for each medical condition and for each antidepressant type. The pharmacological interventions were significantly more effective than the placebo or treatment as usual in preventing the onset of a depressive episode with a pooled OR of OR 0.37 CI (95% CI 0.24-0.54)

~~0.35 (95% CI: 0.23, 0.50).~~

**(Fig 2 about here)**

The trials that used only antidepressants (22 trials, participants=1958,) had a pooled OR of 0.29 (95% CI: 0.18, 0.46). The overall effect size for Selective Serotonin Reuptake Inhibitors (SSRIs) was also significantly better than the placebo in preventing depression with an OR estimate of 0.29 (95% CI: 0.17, 0.50).

**(Fig 3 about here)**

Commented [5]: Studies from database searching ( 2479) + studies from other sources (26)

Commented [6]: Table 1 shows 7 hep studies not 8

All Post Stroke Depression (PSD) trials used antidepressants, which were statistically significantly better than placebo in preventing post stroke depression (OR=0.16, 95% CI: 0.05, 0.55). Similarly, pharmacological interventions were more effective in preventing the depressive illness associated with Hepatitis C, (OR=0.561, 95% CI: 0.31, 1.02). The pooled estimates for other conditions are as following: head and neck cancer OR 0·30; (95% CI: 0.13, 0.69), postnatal depression OR= 0.59 (95% CI: 0.20, 1.76]0.33, 1.04), traumatic brain injury OR=0·26 (95% CI: 0.08, 0.84) and acute coronary syndrome OR= 0.56 0.18 (95% CI: [0.07, 4.510.04, 0.86). The pharmacological interventions for preventing depression in the menopause were not statistically significantly associated with prevention of depressive episodes (OR=0.48, 95% CI: 0.28 09, 0.85 2.49) and in the malignant melanoma the summary OR estimate was 0.09 (95% CI: 0.02, 0.50) (figure 2)

The details of the quality assessment using the Cochrane risk of bias tool are shown in figure 4. Fifteen Sixteen studies were classified as having low risk of bias. All studies with low risk of bias used antidepressants with the exception of one article in which Melatonin was used (Madsen et al, 2019). sStudies with low risk of bias used antidepressants and showed a statistically better effect of pharmacological agents in significant association in preventing depression (pooled OR 0.43 ; 95% CI 0.30-0.60) 0.35 (95% CI: 0.23,0.52) (Fig 5). No publication bias was detected on the visual inspection of the funnel plot or trim and fill analysis (see appendix 2and 3)

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**(Figure about 4 here)**

**(Fig 5 about here)**

The NNT for the preventive effect of all pharmacological intervention was seven. In the analysis limited to studies using antidepressants, the NNT was 6 and in studies with low risk of bias the NNT was 8.

**The effect of duration of follow up:**

The duration of intervention varied between 8 to 54 weeks (mean 29.37; SD 16.16 weeks). The meta-regression to adjust for the length of trial follow-up showed that the follow up duration did not have significant effect on the overall effect of the pharmacological interventions (OR .006 (SE 0.012 , P< 0.59; 95% CI -0.03, - 0.01)OR= (0.99; 95% CI: 0.97-1.02)

**Effects of antidepressants on physical health outcomes**

In view of heterogeneity of outcomes as described below and quality of reported data, it was not possible to conduct meta-analysis of this data. We report a summary of these outcomes below.

Five studies (de Knegt et al., 2011; Diez-Quevedo et al., 2011; Klein et al., 2014; Raison et al., 2007; Schaefer et al., 2012) reported the effect of prophylactic antidepressant treatment in response to anti-viral treatments. Four studies found that prophylactic antidepressant treatment did not help to achieve sustained virologic response (de Knegt et al., 2011; Diez-Quevedo et al., 2011; Raison et al., 2007; Schaefer et al., 2012). The use of antidepressant also had no influence on haematological or biochemical parameters or the dosage reduction of either IFN-alpha or ribavirin (de Knegt et al., 2011). Only one study found (Morasco et al., 2007) that the treatment with Paroxetine helped to

achieve a statistically significant sustained viral response (SVR) compared with placebo (SVR on Paroxetine 7/14; 50% versus 2/19; 10.5% on placebo, p=0.019).

Four studies (Klein et al., 2014; Morasco et al., 2007, 2010; Musselman et al., 2001)~~(Klein et al., 2014; Morasco et al., 2010, 2007; Musselman et al., 2001)~~ examined the effect of prophylactic antidepressant treatment on the likelihood of completion of the anti-HCV (Hepatitis C Virus) treatment and adherence with Pegylated Interferon alpha (PEG-IFNα) and Ribavirin. Mussleman et al. (2001) found that Paroxetine treatment significantly decreased the likelihood that interferon alpha therapy would have to be discontinued because of severe depression or related neurotoxic effects (5% in paroxetine as compared to 35% in placebo; relative risk, 0.14 [95% CI 0.05 to 0.85]). However, three studies (Klein et al., 2014; Morasco et al., 2007, 2010)~~(Klein et al., 2014; Morasco et al., 2010, 2007)~~ did not find any beneficial effect on adherence with prescribed PEG-IFNα and Ribavirin treatment for HCV or the likelihood of completing the recommended course of treatment for HCV.

Two studies (Almeida et al., 2006; Robinson et al., 2008) found no beneficial effect of prophylactic antidepressants used in PSD on functioning, on cognitive and disability outcomes or mortality or the duration of hospital stay. Only Zhang et al. (2013) found that the use of Duloxetine was associated with improvement in Mini Mental State Examination (MMSE) scores and activities of daily living. Jorge et al. (2016) reported no beneficial effect of prophylactic Sertraline on a range of cognitive measures including attention, working memory, episodic memory and speed of information processing in patients with traumatic brain injury

**Discussion**

To our knowledge, this is the first systematic review providing a pooled estimate of all pharmacological interventions that have been used for prevention of depression. Majority of pharmacological interventions were used in physical conditions associated with high risk of depression and had significant effect in preventing depression with a medium effect size of OR 0.37 ( CI 0.25-0.54) ~~OR=0.35 (95% CI: 0.23, 0.50 )~~. The analysis limited to studies with low risk of bias showed the same effect size. Antidepressants were used for prevention in 22 trials and had significant effect in prevention of depression (OR=0.29; CI: 0.18, 0.46), which suggests that use of antidepressants may be a viable strategy for the prevention of depression in physical disorders that have high risk of depression.

Previous meta-analyses studied the effects of antidepressants in preventing depression in a single high risk condition e.g. post-stroke depression (Salter et al., 2013) and depression associated with Hepatitis C (Al-Omari et al., 2013)~~(Al-Omari, Cowan, Turner, & Cooper, 2013)~~. These meta-analyses showed that the incidence of depression reduced significantly in post stroke depression (Salter et al., 2013) with prophylactic antidepressants in patients who were free of depression at baseline and in those receiving interferon treatment (Al-Omari et al., 2013) for Hepatitis . The subgroup analysis in the present study for these conditions had broadly similar results. However, comparison of those studies with the results of our present meta-analysis is not appropriate in view of the different outcome measures and methodologies used. Other studies such as Sockol et al. (2013) combined both pharmacological and psychological interventions in the meta-analysis of postnatal depression prevention and cannot be compared with our study.

Our study identified the potential role of antidepressants in preventing the onset of depression in number of high-risk conditions. Other agents reported in the included studies, such as selenium, hormone treatments or Omega-3 fatty acids had little evidence and should not be considered for the future prevention studies.

The antidepressants were effective in preventing depression associated with Hepatitis C treatment and Post stroke depression (PSD), which also had the largest number of trials. According to a recent meta-analysis PSD has a cumulative incidence of up to 52% within 5 years of stroke (Ayerbe et al., 2013)~~(Ayerbe, Ayis, Wolfe, & Rudd, 2013)~~ and is associated with increased mortality and morbidity (Bartoli et al., 2013). A study based on the Danish Stroke Registry found that the early antidepressant treatment was associated with substantially lower all-cause mortality (Mortensen et al., 2015). Chollet et al. (2011) showed that early prescription of fluoxetine with physiotherapy enhanced motor recovery after 3 months in patients with ischaemic stroke and moderate to severe motor deficit, although a recent trial did not find the beneficial effect of Fluoxetine in improving functional outcomes after acute stroke(FOCUS Trial Collaboration, 2019). Similarly, a recent study showed that a follow-up depression diagnosis at any time following Coronary Artery Disease (CAD) was found to be associated with a 2-fold higher risk of death than in patients in whom depression is not diagnosed. Depression more strongly predicted death than any other baseline characteristic, risk factor, comorbidity, severity of CAD, and follow-up events (May et al., 2017). The high burden of disease caused by cardiovascular disease, the potential benefits in preventing depression in these disorders and practical problems in identification and diagnosis of depression following CVA (Cardio Vascular Accident) imply that depression associated with cardiovascular disorders may be a feasible target for prevention in future studies.

**Commented [8]:** FOCUS Trial Collaboration. Effects of fluoxetine on functional outcomes after acute stroke (FOCUS): a pragmatic, double-blind, randomised, controlled trial. Lancet 2019; 393: 265–74

Two previous meta-analyses found that preventative psychological interventions lowered the incidence of depression by about 21% compared with controls (Cuijpers et al., 2008; van Zoonen et al., 2014). This was considered to be clinically relevant effect size. These systematic reviews, however, included a wide range of psychological interventions including cognitive behaviour therapy (CBT), interpersonal therapy and problem solving therapy. Considering that antidepressants are relatively low cost and easy to use in clinical practice, the evidence for the effectiveness of antidepressants may be relatively easy to translate into public health interventions. A combination of the psychotherapy and antidepressants may be more effective in prevention of depression, as is the case in treatment of depression. This should be explored in future studies.

Depression is predicted to rank first for global disease burden, in high-income countries by 2030 (Mathers & Loncar, 2006) and the prevention must be a global priority (Cuijpers et al., 2012). The most effective way of preventing depression was also identified as the top most priority by patients, carers, medical professionals and academics in a recent study by The James Lind Alliance Priority Setting Alliance (James Lind Alliance, 2016) .The prophylactic treatments in high-risk populations associated with physical comorbidity can prove a useful strategy for preventing depression and high morbidity associated with these disorders.

The Numbers Needed to Treat (NNT) for the pharmacological interventions in order to prevent one additional was seven. The use of NNT in this population where the base rate for depression can vary between different conditions is problematic (Stang et al., 2010)~~(Stang, Poole, & Bender, 2010)~~. However, this helps to put the finding in a perspective. The NNT for Warfarin in preventing an ischaemic stroke in patients with atrial fibrillation is 25 (Aguilar & Hart, 2005). The NNT to prevent

one myocardial infarction over 5 years of aspirin use is 118 (US Preventive Services Task Force, 2009). The preventive studies using pharmacological interventions in Psychiatry are rare. One systematic review (Sijbrandij et al., 2015) that examined the pharmacological interventions to prevent trauma related psychiatric disorders based on meta-analysis of both RCTs and cohort studies, found NNT of 11 but the effect was non-significant when only RCTs were included in the sub analysis.

Future research needs to examine the acceptability of antidepressant use by service users to prevent rather than treat the depression before the strategy can be considered for routine clinical practice. All studies used antidepressants in therapeutic doses. It is possible that the dose required for preventing depression is lower than the therapeutic doses, thus further improving the acceptability and tolerability of the antidepressants in prevention of the disorder. Studies testing different doses, with longer follow up periods and adequate reporting of safety and the other relevant outcomes such as disability and quality of life are needed.

**Limitations**: We used comprehensive search strategy and it is unlikely that any published studies were missed. The robust quality criteria to determine the risk of bias including the use of validated measures to exclude depression at the baseline and relatively low heterogeneity are strengths of the present study. We used a broad search criterion to identify all studies that aimed to prevent depression. However, the evidence for prevention is limited to use of pharmacological interventions only in high risk conditions.

The main limitation of the review is the quality of the primary evidence. The statistical heterogeneity was low but the included papers were clinically heterogeneous in terms of participants, underlying physical conditions and duration of follow-up. The total sample size in some conditions was small, e.g. four trials had 218 participants testing three different interventions in Postnatal depression. The short follow up period of about 28 weeks is a major limitation in determining the long term effect of preventive treatments. It is also not clear whether the pharmacological interventions reduced the incidence of depression or only delayed onset. However, both preventing and delaying onset are important from a clinical and public health perspective.

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**Appendix- 2**

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