INPLASY PROTOCOL

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Review Stage at time of this submission: **Preliminary searches.**

Conflicts of interest:
None declared.

The Fragility of Statistically Significant Findings from Depression Randomized Controlled Trials

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Review question / Objective: **The Fragility of Statistically Significant Findings from Depression Randomized Controlled Trials.**
Condition being studied: **Depression is a mental disorder characterized by a range of symptoms, including loss of memory and sleep, decreased energy, feelings of guilt or low mood, disturbed appetite, poor concentration, and an increased risk of suicide. According to a systematic analysis of the Global Burden of Disease Study 2019, depression is recognized as the leading cause of disease burden for mental disorders, accounting for the largest proportion of disability-adjusted life years (DALYs) at 37.3%. The fragility index (FI), which is the minimum number of changes from events to non-events resulting in loss of statistical significance, has been suggested as a means to aid the interpretation of trial results, as the potential inadequacy about robustness of threshold P-value as a tool for reporting binary outcomes in clinical trials. In this systematic review, we want to calculate the FI of randomized controlled trials (RCTs) in depression.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 25 April 2023 and was last updated on 25 April 2023 (registration number INPLASY202340086).

INTRODUCTION

Review question / Objective: **The Fragility of Statistically Significant Findings from Depression Randomized Controlled Trials.**

Rationale: **The fragility index (FI), which is the minimum number of changes from events to non-events resulting in loss of statistical significance, has been suggested as a means to aid the interpretation of trial results, as the potential inadequacy about robustness of threshold P-value as a tool for reporting binary outcomes in clinical trials. In this systematic review, we want to calculate the**

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FI of randomized controlled trials (RCTs) in depression.

Condition being studied: Depression is a mental disorder characterized by a range of symptoms, including loss of memory and sleep, decreased energy, feelings of guilt or low mood, disturbed appetite, poor concentration, and an increased risk of suicide. According to a systematic analysis of the Global Burden of Disease Study 2019, depression is recognized as the leading cause of disease burden for mental disorders, accounting for the largest proportion of disability-adjusted life years (DALYs) at 37.3%. The fragility index (FI), which is the minimum number of changes from events to non-events resulting in loss of statistical significance, has been suggested as a means to aid the interpretation of trial results, as the potential inadequacy about robustness of threshold P-value as a tool for reporting binary outcomes in clinical trials. In this systematic review, we want to calculate the FI of randomized controlled trials (RCTs) in depression.

METHODS

Search strategy: In this systemic review, we will conduct a PubMed search for RCTs related to depression from January 1, 2012, to October 1, 2022, in any language, that was published in any of 35 psychiatry journals belonging to Science Citation Index (SCI) District Q1, or four major general journals (The New England Journal of Medicine, Lancet, JAMA, British Medical Journal). The earlier time frame was established to ensure that the publications selected would be representative of the quality of recent literature.
Journals are selected for the present study based on a combination of the following features: impact factor, specialization in the publication of depression RCTs, and global recognition for consistent publication of influential RCTs over the last decade.
The New England Journal of Medicine, The Lancet, Journal of the American Medical Association, The British Medical Journal, and 35 top journals listed in Psychiatry-Social Sciences Citation Index (SSCI) category updated 2022 in the field of psychiatric medicine focusing primarily on depression.
Key search terms conducted will be "Depress*" or "Dysthymi*" or "Adjustment Disorder*", "Mood Disorder*", "Affective Disorder", "Affective Symptoms", and "randomized controlled trials". Additionally, we will use medical subject headings, in various combinations, supplemented with free text to increase the sensitivity and precision of the search strategy for identifying RCTs.

Participant or population: Depressed people.

Intervention: Without any restriction.

Comparator: Without any restriction.

Study designs to be included: Randomized controlled trial.

Eligibility criteria: Studies will be included if they 1) randomized patients 1:1 into two parallel arms, 2) reported in their abstract at least one statistically significant binary outcome (i.e., a P-value of < 0.05 or a 95% CI that excluded a null value), and 3) mentioned an intervention, outcome, or recruited sample population as being depression or related to dysthymia, anywhere in the title or abstract.

Information sources: In this systemic review, we will conduct a PubMed search for RCTs related to depression from January 1, 2012, to October 1, 2022, in any language, that was published in any of 35 psychiatry journals belonging to Science Citation Index (SCI) District Q1, or four major general journals (The New England Journal of Medicine, Lancet, JAMA, British Medical Journal).
Journals were selected for the present study based on a combination of the following features: impact factor, specialization in the publication of depression RCTs, and global recognition for consistent publication of influential RCTs over the last decade.
The New England Journal of Medicine, The Lancet, Journal of the American Medical

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Association, The British Medical Journal, and 35 top journals listed in Psychiatry-Social Sciences Citation Index (SSCI) category updated 2022 in the field of psychiatric medicine focusing primarily on depression.

Main outcome(s): Remission, response.

Additional outcome(s): Incidence, clinically significant change, relapse, recovery.

Data management: Two authors will independently extract the study characteristics from the included studies.

Quality assessment / Risk of bias analysis: Two authors will independently assess the risk of bias for each included trial using the Cochrane Risk of Bias 2 (RoB 2) tool (Sterne et al., 2019) described in the Cochrane Handbook for Systematic Reviews of Interventions, which is consisted of six items of the randomization process, deviations from the intended intervention, missing outcome data, subjective outcome measurement, and selective outcome reporting, with five potential responses: 'Yes', 'Probably Yes' 'No', 'Probably No', and 'No Information'.

Strategy of data synthesis: We will summarize the FI for the included studies using descriptive statistics. In the trials fulfilled the criteria of more than one eligible outcome, we explored the distribution of FIs for different outcomes and conducted a correlation analysis among them.

Subgroup analysis: We will describe the FI of results based on the number of trials site, impact factor, total sample size, the total number of events, the ratio of the enrolled sample size to the screened sample size, comorbidity status, funding status, risk of bias, randomization method, and blinding status.

Sensitivity analysis: We will use linear regression models to evaluate associations between the FI and trial characteristics (the independent variables). For these models, we report the regression coefficients and the 95% CIs. We also determined the correlation between the FI and trial sample size and the total number of events in the trial.

Language restriction: Without any restriction.

Country(ies) involved: China.

Keywords: fragility index; depression; research methodology; sample size.

Contributions of each author:

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