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Insomnia as a predictor of mental disorders: A systematic review and meta-analysis

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Summary

Previous research has identified insomnia as a predictor for the onset of depression. The aim of this meta-analysis is to investigate whether insomnia also predicts the onset of other mental disorders. Longitudinal studies were eligible for inclusion if they investigated insomnia at baseline (including nighttime- and daytime-symptoms) as a predictor of the later onset of psychopathology within a follow-up time-frame of at least 12 months. Thirteen primary studies were included. The results suggest that insomnia is a significant predictor for the onset of depression (10 studies, OR 2.83, CI 1.55-5.17), anxiety (6 studies, OR 3.23, CI 1.52-6.85), alcohol abuse (2 studies, OR 1.35, CI 1.08-1.67, and psychosis (1 study, OR 1.28, CI 1.03-1.59). The overall risk of bias in the primary studies was moderate. This meta-analysis provides evidence that insomnia increases the risk for psychopathology. A future research agenda should include more prospective studies using established diagnostic criteria, assessing insomnia at baseline and including long-term follow-up intervals evaluating a wider range of mental disorders. In addition, prospective long-term interventional studies investigating the efficacy of insomnia treatment for the prevention of mental disorders are called for.

Keywords: insomnia, sleep, psychopathology, depression, anxiety, prevention, risk factor

Abbreviations

CBT-I, cognitive behavioral therapy for insomnia

CI, confidence interval

ICSD, international classification of sleep disorders

OR, odds ratio

Introduction

With a lifetime prevalence of around 25% of the overall population, mental disorders are highly prevalent [1]. Patients with mental disorders suffer from substantial impairments of quality of life and reduced ability to participate in professional and social life [2]. Around 35 to 50% of patients with serious mental illness do not receive treatment in developed countries [3]. After onset of a mental disorder, there is often a delay of several years until first treatment is initiated [4]. In addition, among those who receive treatment, rates of nonresponse and relapse are relatively high: for major depression, for example, relapse rates after cognitive behavior therapy or antidepressant medication are around 50% [5,6].

For economic and practical reasons, it seems reasonable to implement preventive strategies predominantly in those at elevated risk for the onset of a mental disorder. Insomnia, a syndrome characterized by chronic sleep onset and/or sleep continuity problems associated with impairment of daytime functioning, has the potential to serve as an indicator for an elevated risk. Pathophysiologically, insomnia is associated with cognitive and physiological hyperarousal [7,8] increased pre-occupation with sleep [9] and maladaptive sleep-related behavior [10]. Insomnia has been identified as a predictor for the de-novo onset of major depression in two meta-analyses [11,12]. The effect sizes (odds ratios) found in these two meta analyses were 2.60 (95% CI: 1.98-3.42) and 2.27 (95% CI: 1.89-2.71). However, in these previous meta-analyses, some primary studies included participants with only nighttime symptoms without daytime symptoms, though daytime symptoms are a necessary requirement for the diagnosis of insomnia disorder. This is a limitation since in clinical practice, nighttime symptoms such as difficulties initiating and maintaining sleep are commonly reported, but do not require medical or psychological interventions in the absence of any daytime impairment. Clinical insomnia with daytime impairment, in contrast, is treated with either pharmacotherapy or psychotherapy [13]. Insomnia is also a frequent symptom of almost all

mental disorders [14]. Several studies indicate that insomnia may also be a risk factor for other psychiatric symptoms beyond depression, including anxiety and suicide [15].

This opens up the possibility to use treatment of insomnia for the prevention of mental disorders. Insomnia is well treatable, the first-line treatment being cognitive behavioral treatment for insomnia [16–18]. CBT-I is a treatment package including behavioral techniques, relaxation, and cognitive therapy. With CBT-I, insomnia symptoms can be significantly reduced in the short- and long-term [19]. As first step into prevention, the question whether insomnia predicts the later onset of different mental disorders has to be answered.

To the best of our knowledge, no meta-analysis investigating insomnia, including daytime symptoms, as a potential risk factor for different psychiatric symptoms or disorders has yet been performed. The objective of the present study was to quantitatively summarize longitudinal studies investigating whether insomnia at baseline constitutes a risk factor for the later onset of a mental disorder.

Methods

The meta-analysis was performed in accordance with the recommendations of reporting for meta-analyses of observational studies in epidemiology [MOOSE, 20] and the PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions [21]. Two authors (TG and CK) independently performed the literature search, screened all titles and, where applicable, the abstracts and full texts of potentially eligible studies, and extracted relevant data for the analyses from the full texts of selected studies. Doubts were discussed together with the first and the last author (EH and CB) and resolved through decision by consensus.

Search Strategy

The primary search was conducted from 1980 to March 2018. The following term was searched for in the abstract or title: ('insomnia') AND (various keywords for different mental disorders combined with 'OR', e.g. 'bipolar OR anxiety OR panic', etc.) AND ('longitudinal' OR 'epidemiolog*' OR 'prospective' OR 'risk factor'). The literature search was performed using the databases PubMed, Medline, PsycInfo, and PsycArticles.

In addition, for insomnia as a predictor of depression, eligible studies from our previous meta-analysis [11] were included. Primary studies from Baglioni et al. [11] that did not meet inclusion criteria of the present meta-analysis, e.g. with regard to the definition of insomnia, were excluded from the present analysis. The search period for this meta-analysis was from 1980 to March 2010. To search for studies on depression published in the period between March 2010 and March 2018, we used the following search term: 'insomnia' AND 'depression' AND 'longitudinal' OR 'epidemiolog*' OR 'prospective' OR 'risk factor'. Appendix S1 reports the full information on the search strategy.

Additional studies were searched by examining the reference lists of eligible publications and screening of recent congress abstracts (Congress of the European sleep research society and joint congress of the American academy of sleep medicine and the Sleep research society since 2014) for potentially eligible studies. Moreover, sleep researchers from the European Insomnia Network were contacted via e-mail to ask for ongoing research in this area. These strategies served to capture non-published literature.

Study Selection

The following inclusion criteria for primary studies were applied:

- **date:** published between 1980 and March 2018. The lower time limit was selected because DSM III was published in 1980 and studies conducted before this date did not have the possibility to refer to modern definitions of mental disorders.

- **language:** published in English, Italian, German, Spanish or French language**.**
- **publication type:** only primary studies were eligible, no reviews, meta-analyses, case reports, comments, or books**.**
- **age:** studies only including participants with age > 18 at baseline
- **insomnia:** Diagnosis of insomnia based on an interview or questionnaire covering both nighttime symptoms (such as sleep onset and sleep maintenance difficulties) as well as daytime symptoms (such as tiredness, reduced concentration and motivation) of the disorder**.**
- **mental disorders:** Diagnosis of mental disorder based on DSM-III or a later version of DSM or ICD, verified via clinical interview or an abnormal score, exceeding the cutoff for pathology, in a validated self-rating questionnaire
- **baseline psychopathology:** studies were included only if participants with indications of a mental disorder other than insomnia at baseline were excluded from the analysis or if the analyses in the primary study were statistically controlled for baseline psychopathology**.**
- **time span:** only longitudinal studies with follow-up periods of at least 12 months were eligible.

The authors of three primary studies were contacted per email because the data provided in their publications were not sufficient to calculate the parameters necessary for the meta-analysis. Two of them responded and provided the missing details.

Data Extraction

The following variables were manually extracted from all included studies: publication year, number of participants at baseline and follow-up(s), number of follow-up measurements, time between baseline and last follow-up, inclusion and exclusion criteria, response rate,

confounding variables controlled for at baseline, mean age of participants, percentage of females in the sample, diagnostic process for insomnia andpsychopathology, odds ratio and corresponding 95% confidence intervals (measure of risk ratio for the onset of psychopathology for participants with insomnia compared to participants without insomnia).

Meta-analytic calculations

Meta-analyses examining the predictive value of presence of insomnia at baseline for presence of psychopathology at follow-up were performed for depression (n = 10), anxiety disorders (n = 6), alcohol abuse (n = 2), and psychotic disorders (n = 1) . Several studies were included with more than one outcome. As an exploratory analysis, a pooled effect size across all mental disorders was performed. If a primary study had more than one follow-up, the last follow-up was used for the analysis. The logarithms (logs) of the odds ratios (ORs) and their 95% confidence intervals (CIs) were used for meta-analytic calculations. Assuming that there is a distribution of true effect sizes rather than a single true effect size, a random-effects model was selected for meta-analytic pooling of the primary studies [22]. As a test for heterogeneity, x^2 tests and the I^2 statistic derived from the x^2 values were used. An alpha error < 0.20 and an I^2 of at least 50% were taken as indicators of heterogeneity. Only in the absence of heterogeneity, it is recommended to use the fixed effects model, as it assumes that all studies share a common true effect size [22].

Assessment of risk of bias

The QUIPS (Quality in Prognosis Studies) Risk of Bias Assessment Instrument for Prognostic Factor Studies was used as a tool for the assessment of risk of bias in the individual studies [23]. The tool provides criteria for assessing risk of bias for each study on six dimensions: study participation, attrition, prognostic factor measurement, outcome measurement,

confounders, and statistical analysis. On the basis of predefined criteria, risk of bias is rated as low, medium or high. For the present study, the assessment tool was applied by two independent raters (TG and CK). After each rater had completed their work, results were compared and disagreements were resolved by discussion with a third rater (CB). Consensus could be reached for all judgements. Cronbach's alpha was calculated as a measure of interrater reliability for the original grading of the two raters. Cronbach's alpha can be interpreted as follows: > 0.7 acceptable reliability, >0.8 good reliability, > 0.9 excellent reliability.

Publication Bias

Furthermore, we tested for potential publication bias using funnel plots and Egger's tests [24]. They were created with the function funnel of the R package 'meta'. In a funnel plot, effect size (in this case, OR) is plotted against a measure of variability (standard error). The plot is usually asymmetrical in the case of publication bias. Egger's test is a statistical test for asymmetry of the funnel plot [24].

Results

The process of study identification, screening for eligibility, and inclusion is shown in figure 1.

Please insert Figure 1

Description of the sample

Thirteen primary studies were included into the meta-analysis (table 1). The total sample (participants with and without insomnia) included 181,798 participants at baseline and 133,967 at the last follow-up time points. Time between baseline and last follow-up was 61 months on average, whereby 5 studies had their last follow-up after 12 months, three studies after 18 months, and the remaining studies had longer follow-up periods of up to 20 years.

Please insert table 1

[25–37]

Main Results

The results of the meta-analysis are shown in figure 2. The main result is that insomnia is a significant predictor for onset of depression (10 studies, OR 2.83, CI 1.55-5.17), anxiety (6 studies, OR 3.23, CI 1.52-6.85), alcohol abuse (2 studies, OR 1.35, CI 1.08-1.67, and psychosis (1 study, OR 1.28, CI 1.03-1.59). In the exploratory analysis across all mental disorders, the model found an OR of 2.60 (CI: 1.70-3.97), indicating that primary insomnia is a significant predictor for later onset of psychopathology. Significant heterogeneity was present for depression, anxiety disorders, and the total sample.

Due to this high heterogeneity, subgroup analyses were performed (Figure 3). Included studies were divided in those with a shorter follow-up duration (12-24 months) and a longer follow up duration (> 24 months). For both depression and anxiety outcomes, heterogeneity was nonsignificant in studies with shorter follow-up durations, but highly significant in studies with longer follow-ups. Insomnia as a predictor of mental disorders was significant for depression and anxiety in shorter follow-up studies and for anxiety in longer follow-up studies, but not for depression in longer follow-up studies.

In addition, primary studies were divided in those including only participants free of any mental disorders at baseline (“pure” studies), and those allowing for comorbidity at baseline

and performing a statistical control. We found 11 "pure" studies and two with statistical control. Insomnia as a predictor of mental disorders remained significant in the sample of 11 "pure" studies. Heterogeneity, however, was still significant in this subgroup.

Please insert Figures 2 and 3

Risk of bias

Results of the risk of bias assessment, based on the QUIPS risk of bias assessment tool, are shown in table 2. The ratings are illustrated in three different colors, where green (happy smiley) indicates a low risk, orange (indifferent smiley) indicates a medium risk, and red (sad smiley) indicates a high risk. Interrater agreement (Cronbach's alpha) was between 0.8 and 1.0 for the six assessment dimensions. The risk of bias arising from the study samples (sample description, recruitment, inclusion and exclusion criteria) was rated as moderate for most studies. Deductions in the quality rating were given because several studies did not sufficiently describe the recruitment process and the criteria for participant inclusion. The most problematic aspect concerning risk of bias was study attrition, since most authors of primary studies did not make attempts to collect information on participants who dropped out. Concerning the prognostic factor and outcome measurement, the most frequent problem was that the handling of missing data (e.g. due to participants skipping questionnaire items) was not reported. Concerning confounding variables, we decided to include only primary studies with either 'pure' insomnia without comorbidity at baseline, or primary studies that documented comorbidity at baseline and statistically controlled for it. Thus, no primary study was rated as having a high risk of bias concerning confounders. However, most studies received the rating 'moderate' instead of 'low', e.g. because only a small range of potential confounders was assessed, or because the validity of the measurement was questionable. Finally, concerning the statistical analysis, risk of bias was rated as low for most studies.

Please insert table 2

Publication bias

Due to the small number of studies for the outcomes alcohol abuse (n=2) and psychotic disorders (n=1), funnel plots and Egger's tests were only created/computed for the outcomes depression and anxiety. The funnel plots are shown in Figure 4. Egger's tests were insignificant, indicating that funnel plots were not asymmetric, for both outcomes (depression: $t = -1.192$, $p = 0.268$; anxiety: $t = -1.268$, $p = 0.274$). However, visual inspection of the funnel plots indicated a certain degree of asymmetry, e.g. that publication bias cannot be excluded.

Please insert Figure 4

Discussion

The present meta-analysis including 13 primary studies evaluated the predictive power of insomnia at baseline for the onset of a mental disorder within the follow-up period. We found that insomnia is a significant predictor for depression, anxiety, and alcohol abuse. One study suggested that insomnia is also a predictor of psychosis. This result remained significant when the analysis was limited to the 11 studies that only included participants without any mental comorbidity at baseline. Another subgroup analysis indicated that high levels of heterogeneity may be attributable to studies with very long follow-up durations (> 24 months), that may be biased due to maturation and history.

To our knowledge, the present study is the first meta-analysis investigating insomnia as a predictor of psychopathology in general. Our findings are in line with our previous meta-analysis [11], which identified insomnia as a predictor of depression. The overall odds ratio for insomnia to predict depression was comparable with the previous publication (odds ratio 2.10 and 2.8). In the present meta-analysis, we extended our previous finding [11], showing that the presence of insomnia at baseline also increased the odds of suffering from anxiety at follow-up. For the other investigated disorders (alcohol abuse, psychosis), the increase in risk was numerically slightly smaller (around factor 1.5) – however, this difference should not be over interpreted, since a statistical comparison between disorders was not performed. The funnel plots highlight that the results of the study by Chen et al. are outliers for depression as well as anxiety (much higher association between insomnia and mental disorders). A potential reason is that in the Chen et al. study, diagnoses were taken from medical records. Using medical records, compared to interviews or questionnaires that were used in the other studies, may potentially have led to an overdiagnosis of anxiety and depression, e.g. for accounting or invoicing reasons. Another potential reason is a difference in the insomnia diagnosis (ICD in the Chen et al. study vs. DSM or questionnaires in others).

In the following paragraphs, different explanations for the association between insomnia and mental disorders will be discussed. The finding that insomnia is a risk factor not only for a specific mental disorder such as depression, but for a wide range of disorders, fits well with the basic idea of 'Research Domain Criteria' [RDOC, 38]. The RDoC authors propose that despite a high variability of observable symptoms, dysfunctions in only a limited number of neurobiological systems underly all or most mental disorders. The finding of the present meta-analysis highlights the importance of the RDoC domain 'arousal'. Hyperarousal, manifesting itself e.g. in increased fast frequency EEG activity or an increased heart rate, is a known biomarker of insomnia [7,8]. Alterations in brain arousal states are also associated with

a number of mental disorders including depression, anxiety disorders, schizophrenia, borderline personality disorder, posttraumatic stress disorder, and addiction [39–41]. Specific interactions of genetic and environmental risk factors contribute to a brain arousal profile that is associated with an increased risk for mental disorders [42]. Most likely, insomnia plays an important part as a risk factor in this process.

The neuroplasticity hypothesis also can, at least in part, explain how insomnia could contribute to depression. According to this hypothesis, a dysfunction of synaptic plasticity is a major pathomechanism of depression [43]. Synaptic plasticity is the neurobiological mechanism by which the brain adapts to learning tasks and an ever changing environment [44]. In short, synapses have the ability to increase or decrease their strength, based on previous activity patterns. Recent research has shown that synaptic plasticity is reduced in patients with acute major depressive disorder [45]. Sleep, in turn, promotes learning and neuroplasticity [46,47]. Taken together, insomnia, which results in chronic sleep restriction, may increase vulnerability for a dysfunction of neuroplasticity as a pathomechanism of depression.

Another potential pathway is sleep's role in emotion regulation. Sleep is important for basic emotional responses such as fear conditioning and fear extinction [48] and also impacts on more complex forms of emotional processing such as the discrimination of threatening and friendly faces [49] and response to reward [50]. Thus, chronic sleep deprivation in the form of insomnia disorder may impair adequate emotional processing and thus increase vulnerability for psychopathology. However, none of the theories mentioned explains very well why a subgroup of patients with insomnia does develop a mental disorder, but another substantial proportion does not.

Compared to the association between insomnia and depression/anxiety, the association with alcohol abuse and psychosis was numerically smaller and, for alcohol abuse, less consistent (one significant and one insignificant result). This may be an incidental finding, since the

sample of primary studies was much smaller for alcohol abuse and psychosis. It may, however, also point to the fact that the nature of association between insomnia and different mental disorders is different. For example, alcohol use may, for some patients with insomnia, be a (dysfunctional) coping mechanism, since better sleep is often expected after the intake of alcoholic beverages the evening. In patients with a specific vulnerability for substance misuse, but not in the majority of patients with insomnia, this may result in alcohol abuse and dependency. For psychosis, in contrast, the nature of the association may be on a more neurobiological level, e.g. mediated via a hyperactivity of the dopaminergic system that has been associated with both sleep difficulties and psychotic experiences [51].

In subgroup analyses, we investigated whether the association between insomnia and mental disorders is different for studies with short-term follow-up (12-24 months) and longer follow-up duration (> 24 months). Interestingly, numerically, insomnia appeared to have a greater effect on short term depression than long term depression, but a greater effect on short term anxiety than long term anxiety. A likely explanation is that this is an artifact attributable to the Chen et al. study, which is an outlier. This study has a greater biasing effect on the long term anxiety outcome than the long term depression outcome, because there are only two studies investigating long term anxiety, but four investigating long term depression.

The present meta-analysis has several strengths and limitations. An important characteristic of our study is that the presence of both daytime and nighttime symptoms of insomnia at baseline was required for the inclusion of primary studies into the meta-analysis. This is in line with current diagnostic criteria of insomnia [52,53]. Daytime symptoms of insomnia are heterogeneous and include tiredness, fatigue, reduced concentration and motivation, depressed or irritable mood as well as impaired functioning and quality of life. The background is that a diagnosis of insomnia should not be made in cases of mild sleep disturbances which do not lead to daytime impairment, or in cases of habitual short sleep, which is a normal variation rather than a disorder. Fifty-one studies were excluded because

they did not meet this criterion, i.e. the authors reported on sleep disturbances only and did not assess daytime symptoms. This finding points to the fact that daytime symptoms of insomnia are frequently neglected in the diagnostic process and treatment planning [54].

Concerning the implementation of research findings into clinical practice, a limitation of this meta-analysis is that it demonstrates a temporal association between insomnia and psychopathology, but does not allow for causal attributions. If insomnia causally contributes to the onset of mental disorders, early treatment of insomnia would be likely to reduce the risk of later psychopathology. However, it cannot be excluded that insomnia is simply an early symptom which is not causally linked to the later onset or progress of a mental illness. In this case, early insomnia treatment would still be needed in order to alleviate the symptoms of insomnia itself - however, benefits in terms of prevention would be limited in this case. In an Australian clinical trial [55] patients with insomnia who did not meet criteria for major depression at baseline were randomized to CBT-I or a placebo intervention. In this trial, CBT-I was delivered in the form of an online self-help program. At 6-month follow-up, the incidence rate of major depressive episode was not significantly different in the two groups. This lack of significant effect may be due to the low total incidence rate (4%), indicating that the follow-up period of 6 months may have been too short to display differences. An alternative explanation is that the intervention was too weak to have a preventive effect. CBT-I was more effective than the placebo in the reduction of subclinical depressive symptoms (i.e., subjects exhibiting some depressive symptoms, but not meeting criteria for major depressive disorder), suggesting that there is some kind of effect on psychopathology beyond the improvement of sleep quality. This important research question needs to be further clarified in interventional studies.

In conclusion, this meta-analysis provides evidence that insomnia increases the odds for the future onset of psychopathology. In our literature search, we found that previous research has focused on depression and anxiety, whereas research into other mental disorders is scarce. In addition, there is a shortage of longitudinal studies. A future research agenda should include more prospective studies with a thorough diagnostic procedure for insomnia (including daytime symptoms) at baseline and long (≥ 2 years) follow-up intervals assessing a wide range of psychopathology. In case of positive findings confirming the role of insomnia as a predictor of psychopathology, more interventional studies investigating the efficacy of insomnia treatment for the prevention of mental disorders are needed.

Practice Points

- Insomnia is a predictor for the future onset of depression, anxiety, and alcohol abuse, and a potential predictor of psychotic symptoms.
- We recommend screening patients with insomnia for mental disorders.
- In the diagnostic process for insomnia and mental disorders in research and clinical practice, we recommend to adhere to diagnostic criteria.
-

Research Agenda

- Novel prospective research with long-term follow-up intervals evaluating insomnia diagnosis as a predictor of a wider range of mental disorders is called for.
- More prospective clinical trials are needed to investigate whether early treatment of insomnia can prevent the onset of mental disorders.

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Figure and Table legends

Table 1 Characteristics of included studies

BDI, Beck Depression Inventory; CIS-R, Clinical Interview Schedule revised; DIS, Diagnostic Interview Schedule (DSM-III) HADS, Hospital Anxiety and Depression Scale; HADS, Hospital Anxiety and Depression Scale; ISI, Insomnia Severity Index; PSQ, Psychosis Screening Questionnaire; SCAN, Schedule for Clinical Assessment in Neuropsychiatry; SPIKE, Structured Psychopathological Interview and Rating of Social Consequences of Psychic Disturbances for Epidemiology

Table 2 Risk of Bias Assessment for included studies

The QUIPS (Quality in Prognosis Studies) Risk of Bias Assessment Instrument for Prognostic Factor Studies was used as a tool for the assessment of risk of bias in the individual studies. This instrument was developed by a work group comprising epidemiologists, statisticians, and clinicians in 2013 [24]. The tool provides criteria for assessing risk of bias for each study on six dimensions: study participation, attrition, prognostic factor measurement, outcome measurement, confounders, and statistical analysis.

Figure 1 Flow of the study search

Flow of search process with study identification, abstract screening, assessment of eligibility and inclusion into the meta-analysis.

Figure 2 Forest plot

Summary of the meta-analysis for the predictive value of insomnia for future psychopathology. CI confidence interval, d effect size Cohen's d, OR odds ratio, se standard error.

Figure 3 Subgroup analyses

CI confidence interval, d effect size Cohen's d, OR odds ratio, se standard error.

A. Included primary studies were divided in those with a shorter follow-up duration (12-24 months) and a longer follow up duration (> 24 months).

B. Primary studies were divided in those including only participants free of any mental disorders at baseline ("pure"), and those allowing for comorbidity at baseline and performing a statistical control ("stat").

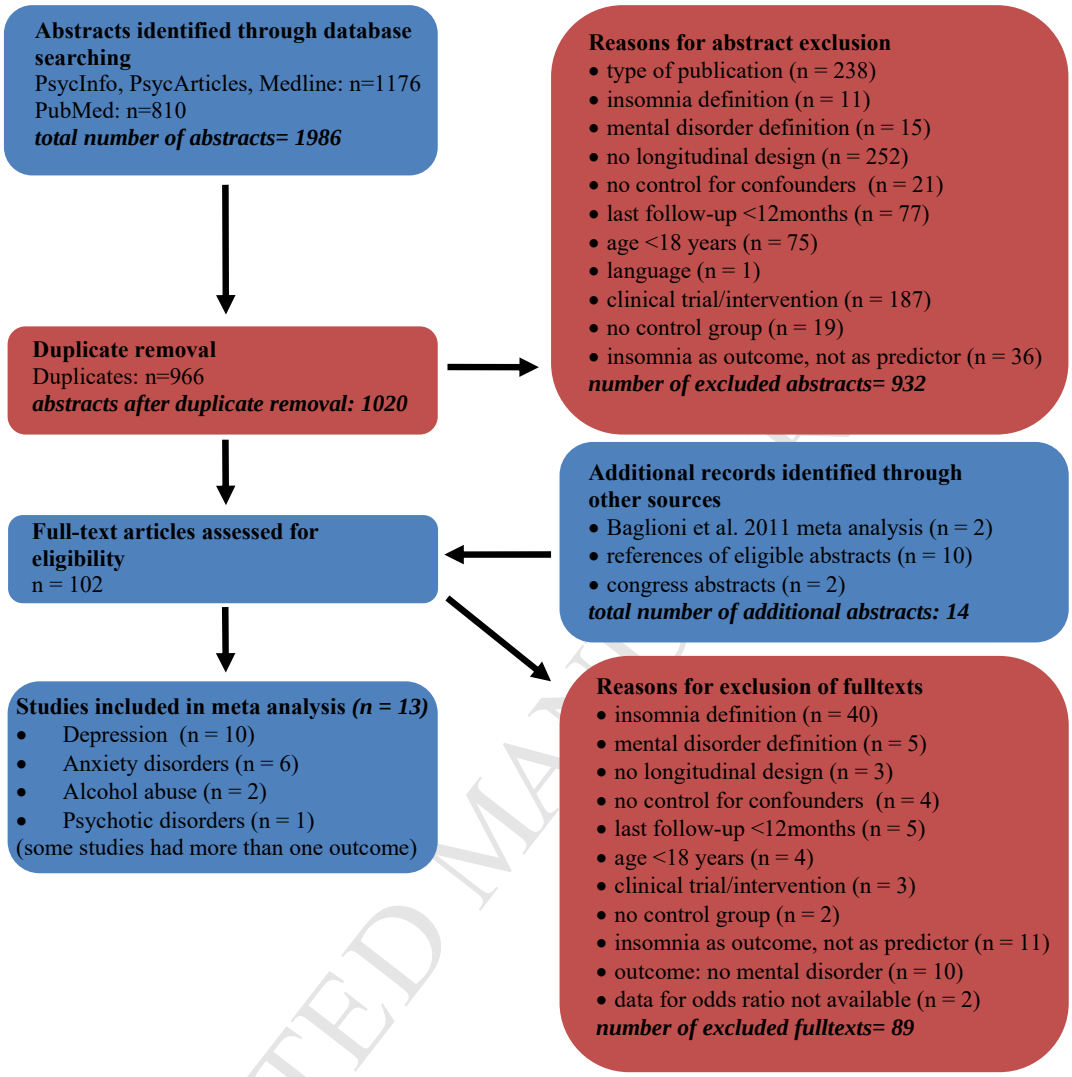
Figure 4 Funnel plots

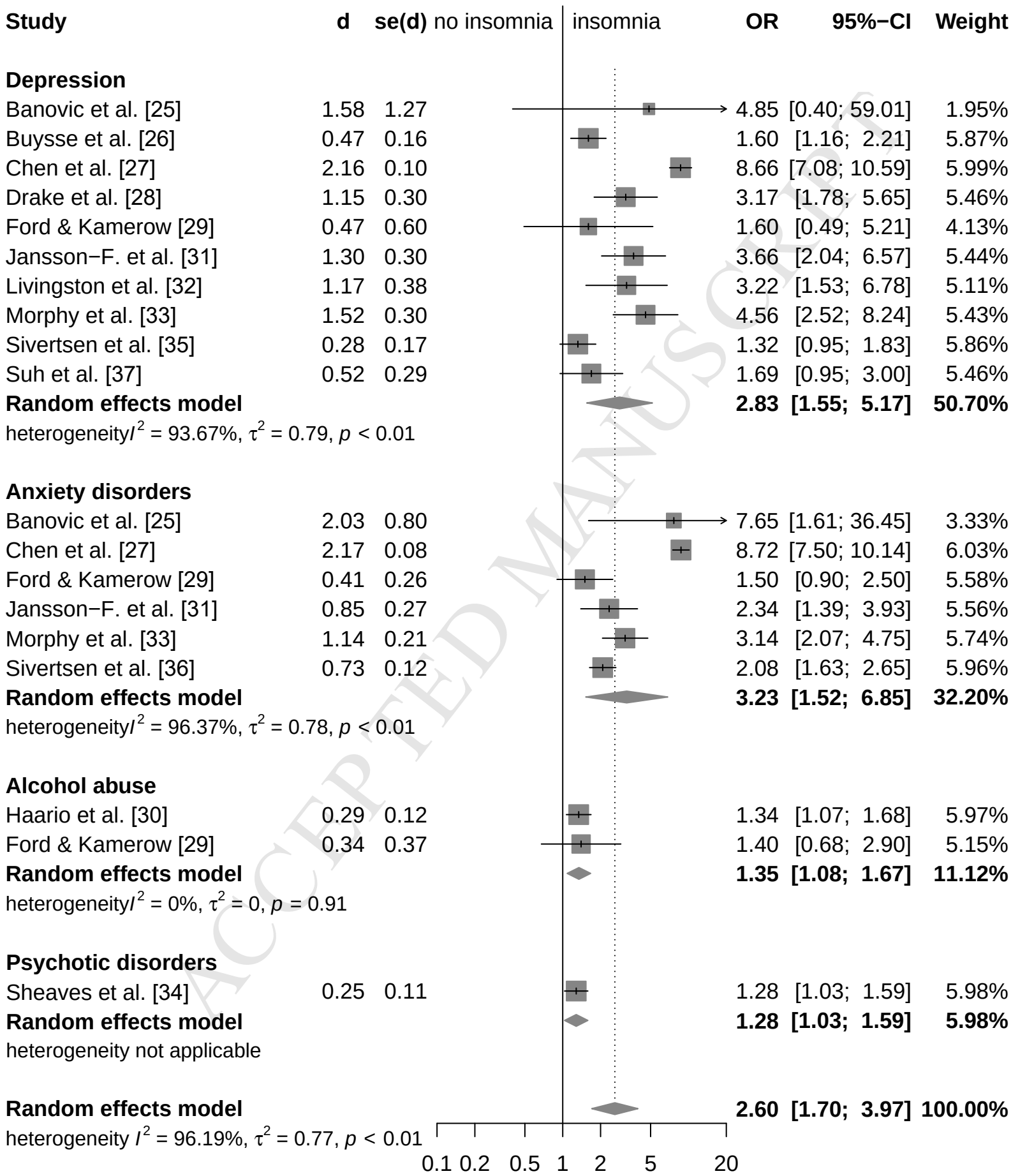
Funnel plots for the assessment of publication bias. Each dot represents one included study. Egger's tests were insignificant, indicating that funnel plots were not asymmetric (depression: $t = -1.192$, $p = 0.268$; anxiety: $t = -1.268$, $p = 0.274$). Vertical line indicates the pooled effect size; funnel indicates 95% confidence intervals.

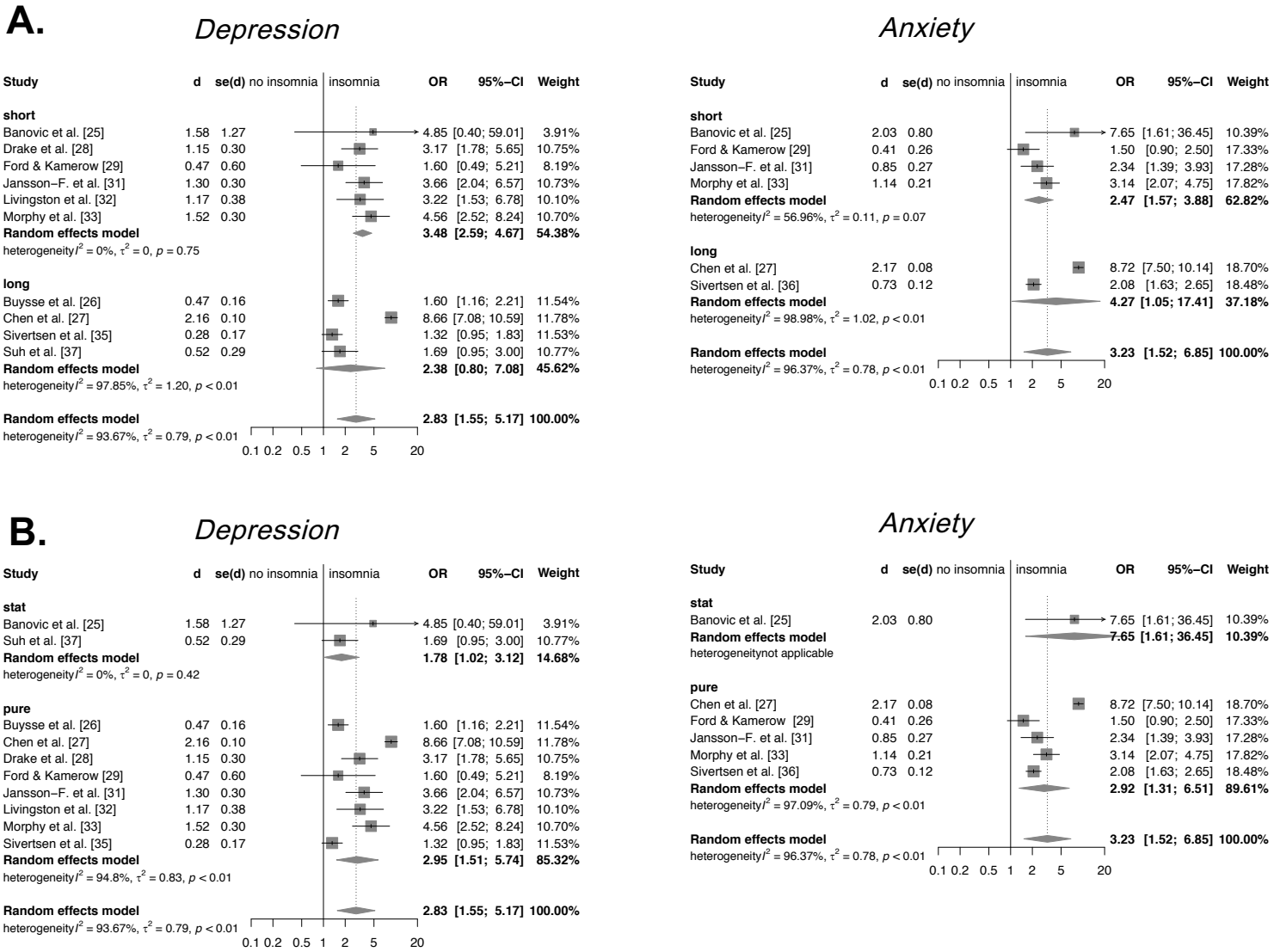
Publication	Insomnia diagnostic method	definition of insomnia daytime symptoms	Psychopathology diagnostic method	last FU (months)	sample	N (baseline)	N (last FU)	Mean age	% female
Banovic et al. [25]	ISI total score >14	according to ISI	depression: HADS-D > 8 anxiety: HADS-A > 8	12	patients with Crohn's disease	57	52	41.2 ± 12.5	55.8
Buysse et al. [26]	clinical interview (DSM-IV criteria)	according to clinical interview (DSM-IV)	depression:SPIKE structured interview	240	representative sample from Zürich, Switzerland	591	275	20-21	n.r.
Chen et al. [27]	ICD-9 diagnosis in medical records	ICD-9 diagnosis in medical records	depression and anxiety: ICD-9 diagnoses in medical records	48	population-based sample from Taiwan	57819	57819	53.7±17.0	55.9
Drake et al. [28]	questionnaire based on DSM-IV	question on daytime interference, answered on 4-point scale	depression: QIDS total score ≥ 11	12	community-based sample from Michigan, USA	2892	2316	n.r.	n.r.
Ford & Kamerow [29]	DIS (based o DSM-III)	question about interference with life	depression, anxiety, alcohol abuse: diagnosis according to DSM-III made in structured interview	12	community-based sample from the USA	10534	7954	n.r.	59.8
Haario et al. [30]	four-item Jenkins Sleep Questionnaire	feeling ‘ "tired and worn out" during day	alcohol abuse:questionnaire on drinking habits based on Finnish Guideline	84	40–60 year-old employees from Helsinki, Finland	8960	7332	40-60	80
Jansson-Frojmark et al. [31]	research diagnostic criteria DSM-IV-TR	list of 10 daytime symptoms rated on 5-point scale	depression: HADS-D > 8 anxiety: HADS-A > 8	18	general population from Sweden	2333	1795	47·1	54.9
Livingston et al. [32]	semi-structured inverview	feeling tired or sleepy during the day	depression:semi-structured inverview	24	persons 65 years and older living at home in London	705	524	n.r.	63.4
Morphy et al. [33]	four-item Jenkins Sleep Questionnaire	feeling ‘ "tired and worn out" during day	depression: HADS-D > 8 anxiety: HADS-A > 8	12	random sample from five general practices in Staffordshire, UK	2662	1589	51.7±17.5	55.9
Sheaves et al. [34]	CIS-R	question about tiredness	psychosis;SCAN interview	18	people aged 16 years and older in the UK	2046	2046	43.9	53.2
Sivertsen et al. [35]	questionnaire based on DSM-IV	impaired work performance caused by insomnia during preceding year	depression: HADS-D > 8	132	general population in Norway (HUNT study)	43045	24715	45.3	56.9
Sivertsen et al. [36]	questionnaire based on DSM-IV	impaired work performance caused by insomnia during preceding year	anxiety: HADS-A > 8	132	general population in Norway (HUNT study)	43045	24715	45.3	56.9
Suh et al. [37]	short questionnaire	feeling unrefreshed in the morning	depression: BDI total score ≥ 16	72	community-based sample from Korea	1282	1089	52.3±7.1	56

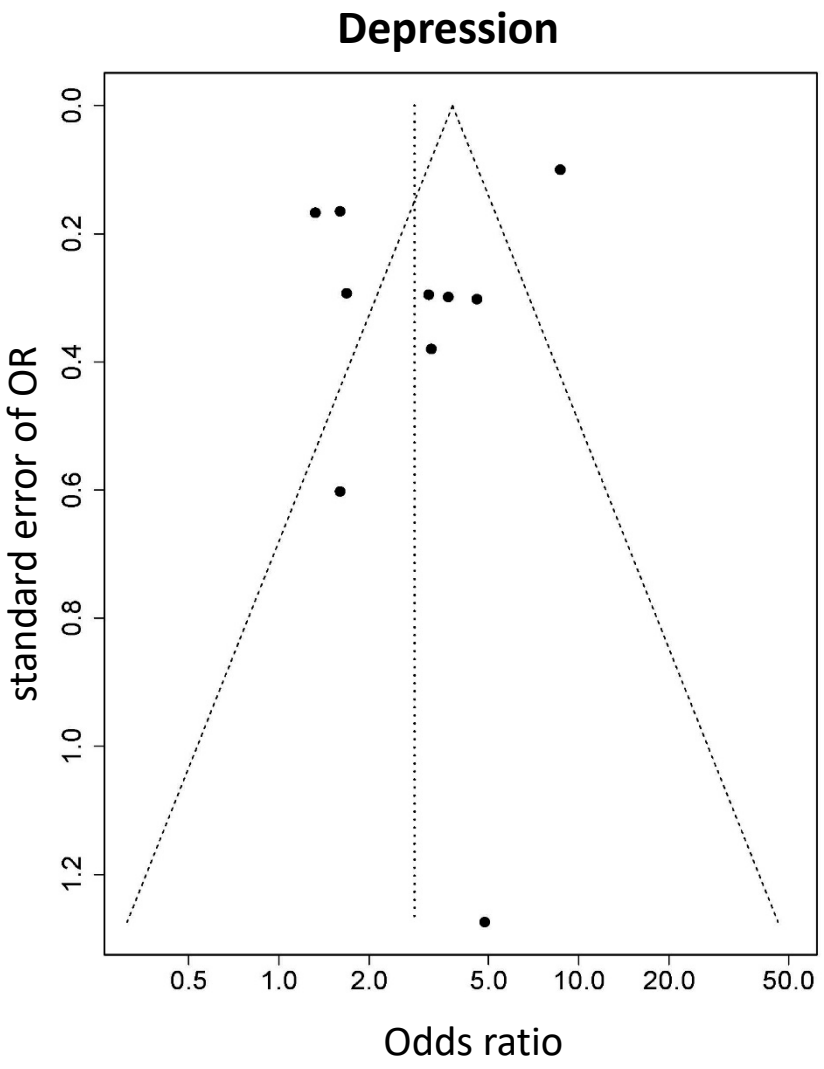
Table 2. Assessment of risk of bias based on the QUIPS risk of bias assessment tool

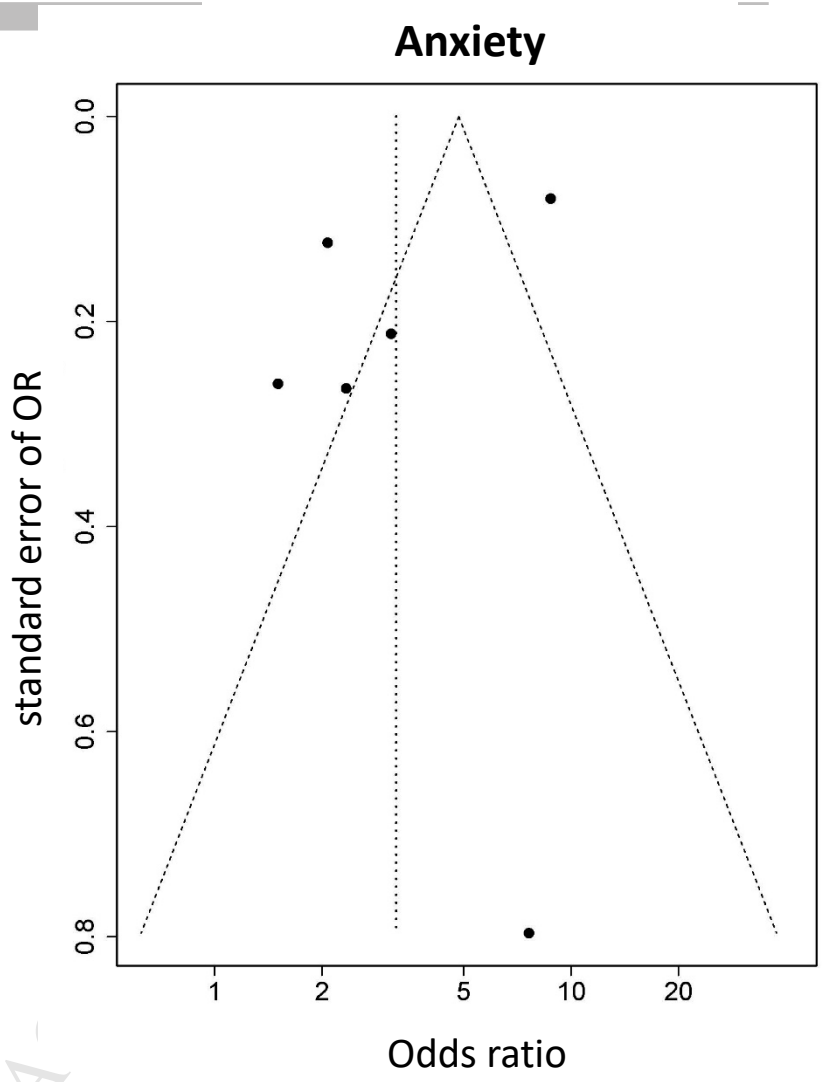
	Sample	Attrition	Prognostic Factor Measurement	Outcome Measurement	Confounders	Statistics
Banovic et al. [25]	☹	☹	😐	☺	😐	😐
Buysse et al. [26]	☺	☹	😐	☺	😐	😐
Chen et al. [27]	☺	☹	😐	😐	😐	☺
Drake et al. [28]	😐	☹	😐	☺	😐	☺
Ford & Kamerow [29]	☺	☹	☹	☺	😐	☺
Haario et al. [30]	😐	☹	😐	😐	☺	😐
Jansson-Frojmark et al. [31]	😐	😐	😐	☺	😐	☺
Livingston et al. [32]	☺	😐	😐	😐	😐	😐
Morphy et al. [33]	😐	😐	😐	😐	😐	☺
Sheaves et al. [34]	😐	☹	😐	☺	😐	😐
Sivertsen et al. [35]	😐	☹	😐	☺	😐	☺
Sivertsen et al. [36]	☺	☹	😐	☺	😐	☺
Suh et al. [37]	😐	😐	😐	☺	😐	☺
Interrater reliability (Cronbach's alpha)	0.9	1.0	0.8	1.0	1.0	1.0






A.
Depression
Study d se(d) no insomnia insomnia OR 95%–CI Weight
short
Banovic et al. [25] 1.58 1.27 4.85 [0.40; 59.01] 3.91%
Drake et al. [28] 1.15 0.30 3.17 [1.78; 5.65] 10.75%
Ford & Kamerow [29] 0.47 0.60 1.60 [0.49; 5.21] 8.19%
Jansson–F. et al. [31] 1.30 0.30 3.66 [2.04; 6.57] 10.73%
Livingston et al. [32] 1.17 0.38 3.22 [1.53; 6.78] 10.10%
Morphy et al. [33] 1.52 0.30 4.56 [2.52; 8.24] 10.70%
Random effects model 3.48 [2.59; 4.67] 54.38%
heterogeneity I^2 = 0%, τ^2 = 0, p = 0.75
long
Buysse et al. [26] 0.47 0.16 1.60 [1.16; 2.21] 11.54%
Chen et al. [27] 2.16 0.10 8.66 [7.08; 10.59] 11.78%
Sivertsen et al. [35] 0.28 0.17 1.32 [0.95; 1.83] 11.53%
Suh et al. [37] 0.52 0.29 1.69 [0.95; 3.00] 10.77%
Random effects model 2.38 [0.80; 7.08] 45.62%
heterogeneity I^2 = 97.85%, τ^2 = 1.20, p < 0.01
Random effects model 2.83 [1.55; 5.17] 100.00%
heterogeneity I^2 = 93.67%, τ^2 = 0.79, p < 0.01
0.1 0.2 0.5 1 2 5 20
Anxiety
Study d se(d) no insomnia insomnia OR 95%–CI Weight
short
Banovic et al. [25] 2.03 0.80 7.65 [1.61; 36.45] 10.39%
Ford & Kamerow [29] 0.41 0.26 1.50 [0.90; 2.50] 17.33%
Jansson–F. et al. [31] 0.85 0.27 2.34 [1.39; 3.93] 17.28%
Morphy et al. [33] 1.14 0.21 3.14 [2.07; 4.75] 17.82%
Random effects model 2.47 [1.57; 3.88] 62.82%
heterogeneity I^2 = 56.96%, τ^2 = 0.11, p = 0.07
long
Chen et al. [27] 2.17 0.08 8.72 [7.50; 10.14] 18.70%
Sivertsen et al. [36] 0.73 0.12 2.08 [1.63; 2.65] 18.48%
Random effects model 4.27 [1.05; 17.41] 37.18%
heterogeneity I^2 = 98.98%, τ^2 = 1.02, p < 0.01
Random effects model 3.23 [1.52; 6.85] 100.00%
heterogeneity I^2 = 96.37%, τ^2 = 0.78, p < 0.01
0.1 0.2 0.5 1 2 5 20
B.
Depression
Study d se(d) no insomnia insomnia OR 95%–CI Weight
stat
Banovic et al. [25] 1.58 1.27 4.85 [0.40; 59.01] 3.91%
Suh et al. [37] 0.52 0.29 1.69 [0.95; 3.00] 10.77%
Random effects model 1.78 [1.02; 3.12] 14.68%
heterogeneity I^2 = 0%, τ^2 = 0, p = 0.42
pure
Buysse et al. [26] 0.47 0.16 1.60 [1.16; 2.21] 11.54%
Chen et al. [27] 2.16 0.10 8.66 [7.08; 10.59] 11.78%
Drake et al. [28] 1.15 0.30 3.17 [1.78; 5.65] 10.75%
Ford & Kamerow [29] 0.47 0.60 1.60 [0.49; 5.21] 8.19%
Jansson–F. et al. [31] 1.30 0.30 3.66 [2.04; 6.57] 10.73%
Livingston et al. [32] 1.17 0.38 3.22 [1.53; 6.78] 10.10%
Morphy et al. [33] 1.52 0.30 4.56 [2.52; 8.24] 10.70%
Sivertsen et al. [35] 0.28 0.17 1.32 [0.95; 1.83] 11.53%
Random effects model 2.95 [1.51; 5.74] 85.32%
heterogeneity I^2 = 94.8%, τ^2 = 0.83, p < 0.01
Random effects model 2.83 [1.55; 5.17] 100.00%
heterogeneity I^2 = 93.67%, τ^2 = 0.79, p < 0.01
0.1 0.2 0.5 1 2 5 20
Anxiety
Study d se(d) no insomnia insomnia OR 95%–CI Weight
stat
Banovic et al. [25] 2.03 0.80 7.65 [1.61; 36.45] 10.39%
Random effects model 7.65 [1.61; 36.45] 10.39%
heterogeneitynot applicable
pure
Chen et al. [27] 2.17 0.08 8.72 [7.50; 10.14] 18.70%
Ford & Kamerow [29] 0.41 0.26 1.50 [0.90; 2.50] 17.33%
Jansson–F. et al. [31] 0.85 0.27 2.34 [1.39; 3.93] 17.28%
Morphy et al. [33] 1.14 0.21 3.14 [2.07; 4.75] 17.82%
Sivertsen et al. [36] 0.73 0.12 2.08 [1.63; 2.65] 18.48%
Random effects model 2.92 [1.31; 6.51] 89.61%
heterogeneity I^2 = 97.09%, τ^2 = 0.79, p < 0.01
Random effects model 3.23 [1.52; 6.85] 100.00%
heterogeneity I^2 = 96.37%, τ^2 = 0.78, p < 0.01
0.1 0.2 0.5 1 2 5 20


Depression
standard error of OR
0.0
0.2
0.4
0.6
0.8
1.0
1.2
0.5
1.0
2.0
5.0
10.0
20.0
50.0
Odds ratio


Anxiety
standard error of OR
0.0
0.2
0.4
0.6
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1
2
5
10
20
Odds ratio