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Minor and subthreshold depressive disorders in Alzheimer's disease: a systematic review and meta-analysis of prevalence studies

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Abstract

Background: Depressive symptoms are common in Alzheimer's disease (AD) and negatively impact patient well-being. The main aim of the present study was to establish summary estimates for the prevalence of minor depressive disorder (MinD) and subthreshold depression in AD and synthesise evidence on prognosis and management of these symptoms in order to inform clinical guidelines.

Methods: Systematic review and meta-analysis of cross-sectional and longitudinal studies of prevalence, prognosis, and treatments for minor and subthreshold depression in AD. We searched MEDLINE, Embase, PsycINFO and CINAHL. We included studies that reported prevalence of subthreshold depressive disorders and those reporting data on validity of diagnostic criteria, mechanisms, or randomised controlled clinical trials (RCTs) testing effectiveness of interventions. Estimates of prevalence were pooled using random-effects meta-analyses. Two authors screened articles and independently extracted data on study characteristics.

Results: We reviewed 5671 abstracts, retrieved 621 full text articles and included a total of 15 studies. Pooling data from 10 studies showed that prevalence for MinD in AD was 22.0% (95% CI 16.0 to 28.0). Prevalence for a clinical diagnosis of MinD (DSM-III-R and DSM-IV) was 26.0% (95% CI 20.0 to 32.0; 6 studies). People with MinD experienced higher levels of neuropsychiatric symptoms, functional and cognitive decline, although studies remain cross-sectional. Neither sertraline nor a carer intervention were effective in reducing symptoms.

Conclusion: This review finds that MinD is prevalent in people with a diagnosis of AD and requires clinical attention. Research is warranted to develop effective interventions to treat and prevent these symptoms.

Declarations of interest:

There are no known conflicts of interest.

There are currently over 50 million people living with dementia globally, with the number of those affected expected to increase to 66 million by 2030 (Prince et al. 2013). Alzheimer's disease (AD) is the most common form of dementia and a leading cause of disability for older people (Di Iulio et al. 2010). Comorbid depression and AD decrease quality of life for people with dementia (Starkstein et al. 2005), increase risk of earlier care home admission (Gaugler et al. 2009) and reduce life expectancy (Burns et al. 1991). Meta-analytic data of prevalence of major depression in AD indicate that these symptoms are common, with rates varying from 12.7% to 42% depending on type of diagnostic criteria used (Asmer et al. 2018, Chi et al. 2015).

Depressive symptoms are a major source of psychological distress for people living with AD, they are persistent and limit individuals' ability to function independently (Fritze et al. 2011). Both major and minor depressive disorder (MinD) in older people are underdiagnosed and can be difficult to recognise (Amore et al. 2007). Although both minor and subthreshold depression are highly prevalent in older people (Polyakova et al. 2014), we currently know very little about these syndromes in AD. This is important given that MinD increases risk of suicidal ideation and developing symptoms of major depression (Meeks et al. 2011).

There is currently wide heterogeneity in the definition and diagnostic criteria of MinD and subthreshold depressive disorders (Rodríguez et al. 2012). MinD is usually defined according to DSM-IV criteria, reflecting a mood-disturbance that requires between 2 and 4 depressive symptoms to be present inclusive of depressed mood or loss of interest or pleasure (Rodriguez et al. 2012). Although these symptoms do not fulfil symptom criteria of major depression they are still associated with greater healthcare utilisation (Chachamovich et al. 2008), predisposing older people to higher levels of disability (Hybels et al. 2001). Therefore having a clear understanding of the epidemiology of MinD and subthreshold depression in AD is warranted. Currently we have limited knowledge about who is more likely to be at

risk, and how these symptoms are managed. Evidence for treating these symptoms is important for informing clinical guidelines.

The aim of the present study was to systematically review worldwide evidence on MinD and subthreshold depressive disorders in AD; more specifically their epidemiology (prevalence and incidence), prognosis and management approaches in order to inform clinicians and future research in the area. A secondary objective was to review evidence on the validity of diagnostic criteria, and any potential mechanisms associated with MinD in this population to identify nosological implications of these disorders.

Method

Search strategy and study eligibility

We searched four main healthcare databases; Medline, EMBASE, PsycINFO and CINAHL. Additionally, we searched, the Cochrane library, national and international trial registers, grey literature and conference proceedings with no restriction on the year of study. Database searching was completed in April 2017. Reference lists of all studies meeting inclusion criteria were examined, as well as review papers on AD and depression. We used a comprehensive list of search terms for minor depression (i.e. minor depressive disorder; subthreshold depression; non-major depression; combined with AD standardised search terms) to ensure no studies were missed (see Supplementary Appendix Figure 1 for the full search strategy).

Two reviewers (E.S.V., R.T.) independently screened all titles and abstracts. The study inclusion criteria were the following: (1) articles that included people with a diagnosis of AD; (2) articles that involved only patients with a current degree of clinically significant minor or subthreshold depression or MinD using clinical diagnostic criteria or a specific cut-off point based on a standardised well-validated scale of depression, and (3) provided data on prevalence and/or incidence of MinD and subthreshold depressive disorders. We included

any cross-sectional, longitudinal study or randomised controlled trial (RCT) reporting on: a) risk factors; b) prognosis; c) mechanisms; d) management approaches and e) validity of diagnostic criteria. We excluded studies that did not report: (1) a cut-off point for MinD, or (2) separate data for people with MinD and AD. Any disagreement was discussed with a third author (V.O.). Ten authors were contacted for further information with three providing additional data.

Data extraction and quality assessment

Two reviewers (E.S.V., R.T.) extracted data independently which included: author, year of publication, sample characteristics, diagnostic criteria or instruments used to diagnose MinD, and mean prevalence and confidence intervals. For studies where standard errors or confidence intervals were not reported, we derived these using standardised procedures (using numerator, and denominator data to obtain Wilson Intervals) (Brown et al. 2001). All data extraction was conducted independently by two authors.

Quality and risk of bias

Studies were evaluated independently by two reviewers (E.S.V., R.T.) on quality and risk of bias with disagreements resolved through discussion with the third reviewer (VO). Prevalence studies were assessed on 4 key domains: selection bias, description of sample, diagnosis of MinD and subthreshold depression, and quality of statistical analysis. Study quality was rated as high, moderate or low (see Table 1 Quality criteria of prevalence studies).

Data synthesis and analysis of prevalence of MinD in AD

Eight out of the 10 studies reported estimates for one time point only for the same participants. In the two prospective cohort studies we used baseline estimates or when these were not provided, the prevalence of the first time point. To examine whether pooled prevalence estimates varied by diagnostic method we performed two different random-effects

meta-analyses (Borenstein et al. 2010). The first included all studies regardless of diagnostic method and the second only studies using Diagnostic and Statistical Manual (DSM) - based criteria. Prevalence estimates were transformed using Freeman-Tukey double arcsine transformation and entered into the meta-analysis with their corresponding standard errors. Heterogeneity was assessed using the I^2 statistic. Stata (version 13, metaprop command) was used to perform the meta-analysis. Publication bias was examined using a funnel plot and an Egger's test (Sterne and Egger, 2001).

Results

Electronic and hand searches identified a total of 5765 records. After removing duplicates and clearly irrelevant articles, 621 papers remained to be screened. Of these, 584 were excluded as not being relevant, leaving 37 papers to be assessed for full eligibility. Of these 37 articles, 22 were excluded (see Supplementary Appendix Table 1 Excluded papers with reasons). A total of 15 articles met the inclusion criteria of which 10 reported prevalence data (see Figure 1 for details of the search process).

Characteristics of included studies

Diagnosis of MinD

Two studies used either DSM-III-R (APA, 1987) or DSM-IV (APA, 1994) criteria to diagnose MinD (Hargrave et al. 2000, Lyketsos et al. 1997a); three studies used DSM-based criteria in combination with a Structured Clinical Interview for DSM (SCID) (Lee et al. 2016, Starkstein et al. 2005, 2011). One study (Lyketsos et al. 1997b) used DSM-IV criteria alongside scores on the Cornell Scale for Depression in Dementia (CSDD; cut-off >6; Alexopoulous et al. 1988). Vida et al. (1994) applied Research Diagnostic Criteria (RDC; Spitzer et al. 1984) and Mormont et al. (2014) diagnosed MinD by administering the Zung Self-Rating Depression Scale (Zung, 1965), as a structured interview (cut-off between 50 and 59). The remaining studies (Li et al. 2001, Gilley et al. 2004) used the Hamilton Depression

Rating Scale (Hamilton, 1960) but with different cut-offs (8-16 and <15). For further details of Characteristics of studies see Table 2 (Supplementary Appendix).

The 5 studies reporting on outcomes other than prevalence used similar diagnostic approaches: Drye et al. (2011) used DSM-IV criteria; Teri et al. (1997) a combination of DSM-III-R and RDC (Spitzer et al. 1984), and Ballard et al. (1996) RDC criteria. Lebedeva et al. (2014) used the Geriatric Depression Scale (GDS, Yesavage et al. 1983); (first cohort - cut-off between 1 and 5; second cohort - cut-off not provided). Lee at al. (2014) used DSM-IV criteria in combination with the SCID (see Tables 3-5 in Supplementary Material for Characteristics of studies).

Primary outcomes

Prevalence and incidence of MinD in AD

Prevalence varied across studies ranging from 9.4% to 38.8% (95% Confidence Intervals (CI): 6.8-12.9 to 35-42.9). Meta-analytic pooling yielded a prevalence of 22.0% (95% CI: 16–28, 10 studies, n=3326; see Figure 2) when all eligible studies were included; with substantial heterogeneity between estimates I^2= 93.2%. When analyses were restricted to studies using a clinical diagnosis of MinD (DSM-based criteria) prevalence was 26% (95% CI: 20-32, 6 studies, n=2768; see Figure 3) with high heterogeneity I^2=90.6%.

Prevalence in studies using DSM-based criteria ranged from 16.7% to 38.8% (95% CI: 10.5- 24.6 to 35-42.9) with lower estimates in studies using screening tools. For the HDRS, estimates ranged from 9.4% to 13.2% (95% CI: 6.8-12.9 to 7.3-22.6) whereas for the Zung SDS estimates ranged from 19% at baseline (95% CI: 12.2-27.7) and 11% (95% CI: 11.5-19.4) at 3-month follow-up (29). Only one study reported incidence of MinD in AD (Ballard et al. 1996; n=63). Using RDC criteria incidence of MinD at one-year follow-up was 29.8% (95% CI: 18-46.9).

We performed a sensitivity analysis by including only high quality studies. When only studies of low risk of bias were considered prevalence of MinD was 24% (95% CI: 17-32); with high heterogeneity still evident I^2=95.8%. Visual inspection of the funnel plot, and formal testing via the Egger's test (p=0.934) indicated that publication bias or small study effects were unlikely to have affected the results (see Supplementary Appendix, Figure 2).

Quality of prevalence studies

Overall, we rated the quality of the evidence as moderate. Most studies were rated as being of high quality on diagnostic methods (60%) and description of study samples (70%). For the majority of studies selection bias was moderate (70%); where details of why participants declined participation in the study were not reported. However, ninety per cent (90%) of the included papers scored low on statistical analysis. This was due to studies not providing a sample size justification, or data on precision of estimates (e.g. standard error or CIs) which decreases confidence in the results (see Supplementary Appendix Table 6 Quality ratings of prevalence studies).

Secondary outcomes

MinD at different stages of AD and effects of disclosure of diagnosis

Two studies assessed whether prevalence of MinD is associated with dementia severity. In the cross-sectional study by Starkstein et al. (2005) prevalence of MinD (DSM-III-R in combination with SCID) differed by AD severity (n=670, p<0.01); with estimates increasing from 21% in moderate AD to 45% in the severe stages. The second cross-sectional study (Lyketsos, 1997b) found no differences in prevalence (DSM-IV criteria) across mild, moderate and severe stages (n=109, p=0.21). The prospective study by Mormont et al. (2014) examined the association between disclosure of AD diagnosis and MinD (Zung SDS); there were no differences on diagnostic rates of MinD after 3 months of disclosure of dementia diagnosis (n=96, p=0.57).

Clinical correlates of MinD in AD

Three studies investigated clinical correlates of MinD in mild to severe AD. Two studies by Starkstein et al. (2005, 2011) found that MinD (DSM-III-R; DSM-IV and SCID) was associated with higher levels of neuropsychiatric symptoms and functional decline ($p < 0.01$). In the Starkstein et al. (2011) study those with MinD had significantly lower scores on cognition ($p<0.0001$). In the cross-sectional study by Lyketsos et al. (1997b) MinD (DSM-IV criteria) was associated with greater non-mood behavioural disturbances ($p<0.04$).

Genetic and neurobiological mechanisms of MinD in AD

Lyketsos et al. (1997a) examined the cross-sectional association of the Apolipoprotein E (APOE) genotype and phenotypic expression of MinD (DSM-IV criteria); frequency of MinD did not differ by APOE genotype (E2/E3, E2/E4, E3/E3, E3/E4 and E4/E4; in all cases $p > 0.10$). Two cross-sectional studies explored neuroanatomical changes associated with MinD. In the study by Lebedeva et al. (2014) MinD (diagnosed by GDS) was associated with thinning in the left temporal and inferior parietal regions ($p<0.001$). In the second cohort of the same study, MinD (diagnosed using the CSDD) was predictive of cortical thinning of both temporal and parietal regions. In those with MinD there was a negative correlation between cerebrospinal fluid (CSF) and cortical thickness (clusterwise p value (CWP) = 0.008). Lee at al. (2014) however found no significant differences in medial prefrontal, limbic or WML volumes of patients with or without MinD (DSM-IV and SCID) in a sample of 27 people with mild AD.

Validity of diagnostic criteria of MinD in AD

We found one cross-sectional study (Starkstein et al. 2011) investigating the validity of the DSM-IV diagnostic criteria for both major and MinD in AD. Latent cluster analysis (LCA) in 971 outpatients with mild to severe AD demonstrated three clusters of symptoms representing major depression (cluster 3), minor depression (cluster 2) and no depression

(cluster 1). Although overall there was evidence of validity of the diagnostic criteria, results indicated that MinD in AD may be an heterogeneous condition, and that patients with MinD may experience higher levels of apathy.

Management approaches of MinD in AD

The Depression in Alzheimer's Disease Study-2 (DIADS-2) (Rosenberg et al. 2010, Drye et al. 2011) was a 24-week randomised, parallel, placebo controlled clinical trial evaluating efficacy of sertraline in people with mild to moderate AD that also met criteria for MinD (DSM-IV). Sertraline was not superior to placebo on the modified Alzheimer's Disease Cooperative Study Clinical Global Impression of Change (mADCS-CGIC) at 12 weeks (odds ratio (OR) sertraline=1.1, 95% CI: 0.4-3.1); or on CSDD scores at 12 (difference=-3, 95% CI: -6.5-0.8) and 24 weeks (difference= -0.2, 95% CI: -4-3.5) or on proportion of patients in remission at 12 (OR sertraline=1.7, 95%CI: 0.5-6.5) or 24 weeks (OR sertraline=0.8, 95% CI: 0.3-2.9). One small feasibility RCT (n=72) of a carer-delivered intervention aimed at reducing depressive symptoms in people with moderate AD and MinD (DSM-III-R and RDC) found no significant differences between treatment and control conditions on rates of MinD diagnosis post treatment (9 weeks) (Teri et al. 1997).

Discussion

Prevalence of MinD and subthreshold depression in AD

This is the first systematic review and meta-analysis to investigate prevalence of MinD and subthreshold depressive disorders in AD. We were able to estimate prevalence of MinD by including 10 studies from 5 different countries including 3326 participants in our meta-analyses. To reflect the heterogeneity of methods used to diagnose MinD and subthreshold depressive disorders we report two prevalence estimates. Pooled prevalence across all studies using both screening tools and diagnostic criteria was 22% (95% CI: 16–28) whereas the estimate increased to 26% (95% CI: 20-32) when pooling only studies using DSM criteria.

These results show that prevalence of MinD is common in people living with a diagnosis of AD. This is particularly relevant considering that prevalence of AD is projected to continue to increase (Ahmadi-Abhari et al. 2017). Given the high prevalence found in our meta-analysis, more psychological resources including early assessment and prevention strategies for depression should be allocated for people living with a diagnosis of AD, in line with recent clinical guidelines (NICE, 2018).

Our findings are similar to prevalence meta-analyses of major depression in AD (Asmer et al. 2018, Chi et al. 2015) where type of diagnostic method was found to influence prevalence estimates. Screening tools, however, such as the HDRS (Hamilton, 1960) or the Zung self-rating depression scale (Zung, 1965) consistently tend to be associated with lower estimates and may underestimate prevalence of both minor and major depression in this group. There was substantial variation in prevalence rates, which ranged from 9.4% up to 38.8% across all studies. This variation may depend not only on the approach used to diagnose MinD but also on samples tested, or dementia severity, which varied across studies. Given the lack of population-based studies in the area, it is likely that prevalence of MinD is overestimated. Our meta-analysis by method of assessment, and study quality did not lower heterogeneity across studies indicating that overall heterogeneity can not be explained by differences in study quality, diagnostic systems, scales or cut-off scores used.

Our findings mirror the same pattern of major depression prevalence rates where diagnostic criteria are an important source of variation. Chi et al. (2015) for example report that the prevalence of major depression in AD based on DSM criteria is 12.7% (95% CI: 8.8-17.8); with rates increasing to 42% (97% CI: 38-45) when using AD specific criteria (Olin et al. 2002). These findings suggest that general population approaches in both major and minor depression in AD are potentially underestimating prevalence and that the more disease specific the diagnostic approach, the higher the estimate (McCabe et al. 2006). Similar to

reviews in the general population (Rodríguez et al., 2012) we found evidence of heterogeneous definitions and diagnostic criteria for both MinD and subthreshold depression, with minor depression mostly defined by DSM-IV criteria.

Our prevalence estimates are similar to rates of MinD in people with mild cognitive impairment (MCI). Polyakova et al. (2014) have reported a point prevalence of MinD of 26.5% in MCI in a 3-year longitudinal study and an estimate of 17.2% in a community based study using DSM criteria. These estimates alongside our results suggest that MinD is generally more frequent in older people with cognitive impairment compared to cognitively healthy older people for which MinD estimates range from 10.4% in the community to 14.4% in medical settings (Polyakova et al. 2014).

Risk, prognosis and management of MinD and subthreshold depression in AD

We found very little evidence to inform who is more likely to be at risk for MinD in AD similarly to major depression in this population (Steck et al. 2018). The pathogenesis of MinD is likely to be multifactorial, with different disease and non-disease specific factors contributing to symptoms. With regard to potential neuroanatomical mechanisms, although one study found that cortical thinning in left parietal and temporal brain regions may be implicated in the pathogenesis of MinD in AD (Lebedeva et al. 2014), current research does not allow us to draw any conclusions about the neuroanatomical mechanisms associated with MinD.

We found a small set of cross-sectional studies showing that MinD may be equally distressing in AD as for the general population of older people (Rivas Rodriguez et al. 2012) by being associated with greater neuropsychiatric symptoms, and accelerating functional and cognitive decline (Starkstein et al. 2005, 2011, Lyketsos et al. 1997b). Although informative these findings are cross-sectional therefore clinical studies will be important to be able to assess the impact of these symptoms on prognosis of AD.

We found that evidence base of treatments in MinD is limited. One RCT on effectiveness of sertraline found no significant differences between treatment versus placebo (DIADS-2 study, Rosenberg et al. 2010) in line with evidence on major depression in AD (Orgeta et al. 2017). Teri et al. (1997) examined two behavioural interventions in a small feasibility RCT. Although authors reported a significant overall improvement for the whole sample (people with both major and minor depression) there was no effect on MinD remission. Given that this study was small, testing feasibility of behavioural carer-led approaches, full-scale clinical effectiveness trials of behavioural interventions for treating depressive symptoms in AD are required.

Limitations

Most studies reporting on prevalence of MinD in AD recruited patients from dementia clinics or research settings. Selecting participants via service utilisation, may have biased results towards more severe cases, our findings therefore may have been influenced by selection bias. We did not set a minimum population size for included studies and given that samples in some studies were small and not population-based, the prevalence estimate is prone to be unstable. We used a broader diagnostic category of subthreshold depressive disorders and therefore included studies that did not use diagnostic criteria for MinD but a specific cut-off point, which differed between studies.

Eight out of 10 studies employed cross-sectional designs, and only one provided justification of sample size. Repeated assessment of the syndrome and information on the range of values within which the estimate is contained would have provided more reliable data. To address this, we contacted original authors; and we were able to collect confidence intervals for 3 papers. Other values were derived from data provided in the original investigations and to ensure we accommodated for error in the data, we calculated Wilson intervals, which provide more reliable estimates (Brown et al. 2001). Although this approach

is considered conservative, our estimates may still underestimate or overestimate prevalence. Nonetheless, most of the included studies used clinical criteria to diagnose MinD, which increases our confidence in the estimates provided. Additionally, many of the studies used a combination of diagnostic criteria, structured interviews and rating tools. Despite limitations, our review provides important information about the prevalence of MinD and subthreshold depressive disorders in AD, indicating that clinically significant symptoms of subthreshold depression are frequent.

Implications for practice and research

Although NICE guidelines do recommend access to low intensity psychological interventions for people with mild to moderate depression and AD (NICE, 2018) research on evaluation of these treatments and access to psychological care remain limited. We found one study evaluating antidepressants for MinD which is inconsistent with clinical guidelines for the general population and for older people (Nice, 2016, Baldwin et al. 2003). Our findings encourage provision of early screening of MinD in people living with AD and an urgent need to develop therapeutic interventions. Future clinical studies are required to assess the socio-economic burden and impact of MinD and subthreshold depressive disorders on disease prognosis.

Conclusions

Our review suggests that MinD is common in people living with AD and that clinicians should be aware of the high prevalence of subthreshold depressive disorders in this population. Future studies exploring factors affecting prevalence of MinD and effectiveness of interventions on managing these symptoms are warranted.

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Ethical guidelines were followed in terms of conduct of this study.

Figure 1. Prisma flow chart of the search process

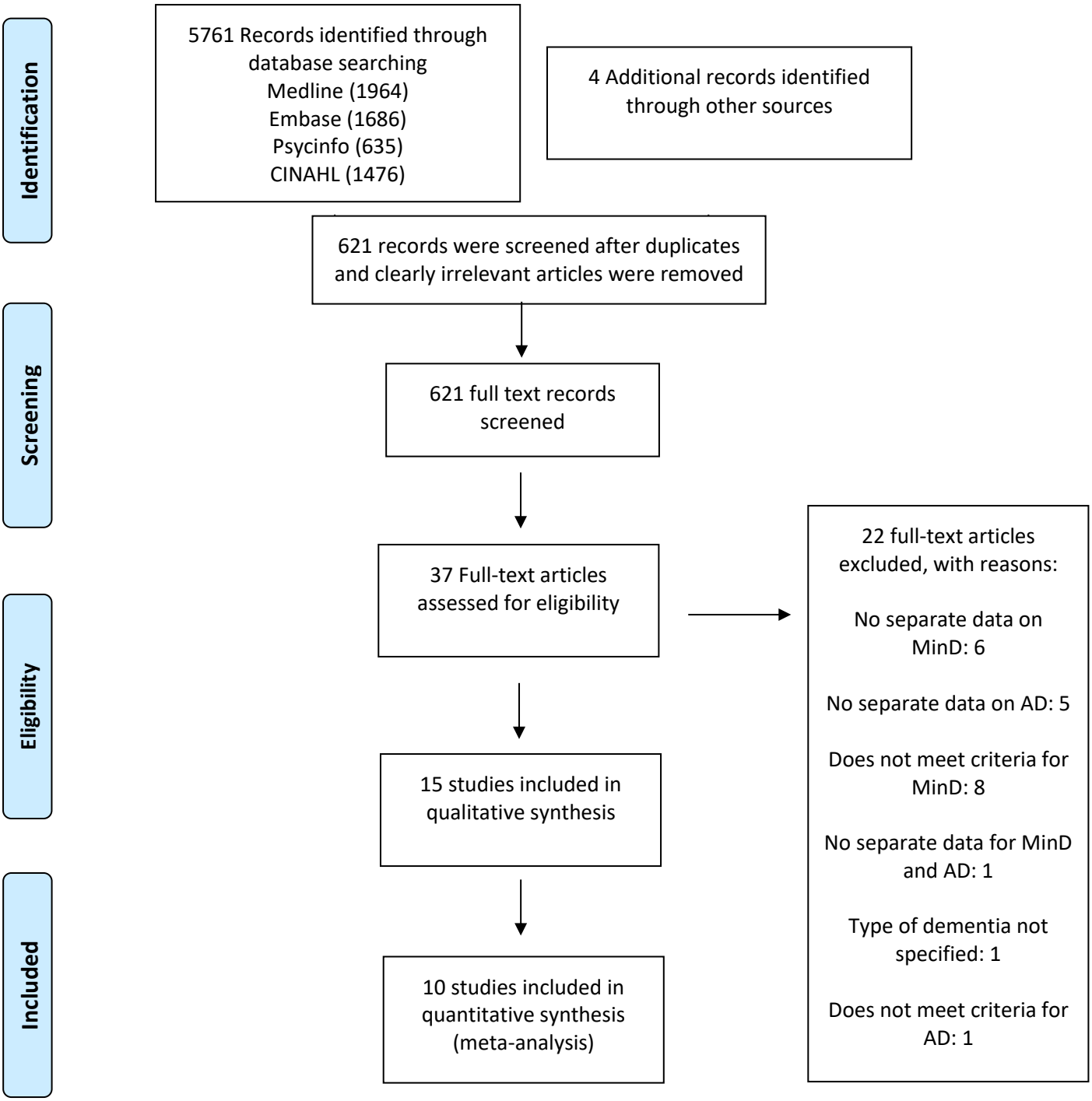

Table 1. Quality criteria of prevalence studies

1) **Sample:** Did the study use participants likely to be representative of the target population? Do the authors provide information on periods of recruitment, method of selection and non-participant rate?
2) **Inclusion and exclusion criteria of the sample**: Did the study pre-specify inclusion and exclusion criteria of the sample? Were these criteria applied to all participants uniformly? Was the study population well defined, e.g.: type of dementia, dementia severity, age, gender, previous depressive disorder?
3) **Standardised diagnoses:** Did the study use standardised criteria or validated scales to assess for minor depression? Were those measures reliable and/or have they been validated? Have they been implemented consistently across all study participants? Was minor depression assessed more than once?
4) **Statistical analysis:** Do the authors provide a sample size justification and description of statistical methods used? Does the study provide unadjusted or adjusted estimates and report error precision (SE or CI)? For longitudinal studies, do the authors give information of loss to follow-up?

Figure 1. Search strategy for the review

1. Depression [MeSH]
2. Mood disorders [MeSH]
3. Adjustment disorders [MeSH]
4. Affective disorder*[key word]
5. Adjustment disorder*[key word]
6. (depress*adj3 (subsyndromal or subthreshold or sub-threshold or subclinical or sub-clinical))[key word]
7. (depress*adj3 insufficient symptom*)[key word]
8. ((minor or mild) adj3 depress*)[key word]
9. (nonmajor or non-major) adj depress*)[key word]
10. ((non-specific or nonspecific) adj depress*)[key word]
11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12. Alzheimers Disease [MeSH]
13. Alzheimer* [key word]
14. 12 or 13
15. 11 and 14

Table 1. Excluded papers with reasons

	Study	Reasons of exclusion
1.	Porta-Etessam (2011)	Prospective observational cohort study to evaluate the effects of depressive symptoms on cognition and function in AD. No separate data on minor depression.
2.	Fritze (2011)	Longitudinal study (1 year follow-up) exploring the course of depressive symptoms in people with dementia. No separate data on AD.
3.	Lind (2006)	Cross sectional study investigating the association between depressive symptoms in people with dementia and white matter changes. Participants did not meet criteria for minor depression. No separate data on AD.
4.	Ballard (1996)	Cross-sectional study of prevalence of minor depression in dementia; no separate data on AD.
5.	Bungener (1996)	Prospective study evaluating emotional disturbances (symptoms of anxiety and depression) in AD. Participants do not meet criteria for minor depression.
6.	Soennesyn (2012)	Prospective cohort study to explore the relationship between white matter hyperintensities and the prevalence and course of depressive symptoms in dementia. No separate data on minor depression and no separate data on AD.
7.	Whitfield (2015)	Cross sectional study exploring the relationship between synaptic zing regulation and depression in people with dementia. No separate data on AD.
8.	Vital (2012)	Cross sectional study to determine the presence of depressive symptoms in AD and its association with physical activity levels. Participants do not meet criteria for minor depression.
9.	Rosness (2010)	Cross sectional study investigating the occurrence of depression in early onset dementia. No separate data on AD.
10.	Janzing (1999)	Longitudinal study to assess the effects of depression on mortality rates for people with dementia. Type of dementia not specified.
11.	Komahashi (1994)	Cross sectional study to assess prevalence of depression in dementia in the Ohira town (Japan). No separate data on AD. Participants do not meet criteria for minor depression.
12.	Mendez (1990)	Retrospective study of the prevalence of psychiatric symptoms in AD. Participants do not meet criteria for minor depression.
13.	Terada (2014)	Cross sectional study examining cerebral blood flow correlates of depressive symptoms in AD. Participants do not meet criteria for minor depression.
14.	Grunblatt (2011)	Longitudinal cohort study examining the role of the choline O-acetyltransferase (CHAT) gene in geriatric depression in AD. No separate data on minor depression.

15.	Castilla-Puentes (2010)	Longitudinal cohort study comparing prevalence of subtypes of depression in patients with dementia. Participants do not meet criteria for minor depression.
16.	Teng (2008)	Descriptive longitudinal cohort study comparing rates of depression in AD using NIMH-dAD to those using other assessment tools. No separate data on minor depression.
17.	Greenwald (1986)	Cross sectional study to determine whether dexamethasone suppression test (DST) can distinguish patients with coexisting AD and depression from those with AD alone. Participants do not meet criteria for minor depression.
18.	Weiner (1997)	Cross sectional study of depressive symptoms reported in AD by patients and carers. Participants do not meet criteria for minor depression.
19.	Magai (2000)	Double blind placebo controlled study to evaluate the efficacy of sertraline for depressive symptoms in late stage AD. No separate data for minor depression.
20.	Linka (2000)	Cross sectional study to examine the prevalence of depressive symptoms in older medical inpatients and to compare the degree of depressive symptomatology in vascular dementia and AD. Participants do not meet criteria for AD.
21.	Starkstein (2005)	Longitudinal study to examine the temporal stability of symptoms of major and minor depression and apathy in AD. No separate data for minor depression.
22.	Petracca (2001)	Double blind placebo controlled study of the efficacy of fluoxetine for depression in AD. No separate data for minor depression.

AD: Alzheimer's disease; **NIMH-dAD:** National Institute of Mental Health, depression of Alzheimer's Disease criteria

Table 2. Characteristics of studies reporting on prevalence of MinD and subthreshold depressive disorder in AD

Study	Sample	Diagnostic criteria for MinD/subthreshold depressive disorder	Reported prevalence of MinD N (%)	Number of high quality ratings (total out of 4)
Cross-sectional studies				
Lee et al. (2016)	Memory clinic outpatients South Korea N=316 Probable AD (NINCDS-ADRDA, DSM-IV) Age: 74 (SD 7.0) MMSE:16.2 (SD 5.7) Mild to moderate AD	Minor Depressive Disorder – DSM-IV/modified SCID for DSM-III-R	64 (20.3%) 95% CI: 16.2 to 25	2
Starkstein et al. (2005)	Memory clinic outpatients Argentina N=670 Probable AD (NINCDS-ADRDA) Age: 72.8 (SD 7.2)* MMSE: 18.4 (SD 6.9)* Mild to severe AD	Minor Depressive Disorder – DSM-III-R based on SCID responses	177 (26.0%) 95% CI: 23.2 to 29.9†	2
Starkstein et al. (2011)	Memory clinic outpatients Argentina N=971 Probable AD (NINCDS-ADRDA) Age: 71.0 (SD 8.4) MMSE: 20.9 (SD 7.1)* Mild to severe AD (CDR)	Minor Depressive Disorder – DSM-IV based on SCID responses	249 (25.7%) 95% CI: 23 to 28.5†	2
Hargrave et al. (2000)	University Dementia Research Center USA N=582 Probable or possible AD (NINCDS-ADRDA) Age: 76.6 (SD 0.5)* Mild AD	Minor Depression – DSM-III-R criteria	226 (38.8%) 95% CI: 35 to 42.9	2

Lyketsos et al. (1997a) ††	Memory clinic outpatients USA N=120 Probable AD (NINCDS-ADRDA) Age: 73.6 (SD 8.5) Mild to moderate AD	Minor Depression - DSM-IV criteria	20 (16.7%) 95% CI: 10.5 to 24.6†	1
Lyketsos et al. (1997b)	Memory clinic outpatients USA N=109 Probable AD (NINCS-ADRDA) Age: 74.4 (SD 7.9) MMSE: 15.0 (SD 6.5, range 0-28) Mild to severe AD (CDR)	Approximate DSM-IV criteria for Minor Depressive Episode (MiDE) (over 1 week) based on CSDD cut off point >6	29 (27%) 95% CI: 18-34†	2
Vida et al. (1994)	Memory clinic outpatients Canada N=26 Probable AD (NINCS-ADRDA) Age: 70.2 (SD 9.5) Mean MMSE: 17.4 (SD 8.1 range 0 to 29) Mild to moderate AD	Research Diagnostic Criteria (RDC) for Minor Depressive Disorder	6 (23.1%) 95% CI: 11 to 42	1
Li et al. (2001)	Clinic outpatients Houston (USA) N=76 AD Possible and Probable AD (DSM-III-R, DSM-IV, NINCDS-ADRDA) Age: 77.1 (7.6) MMSE: 16.4 (SD 8.3, range 0-26) Mild to moderate AD	HDRS (17 items) for minor depression: Cut off between 8 and 16.	10 (13.2%) 95% CI: 7.3 to 22.6	0
Longitudinal studies				
Mormont et al. (2014)	Memory clinic outpatients Belgium N=96	Zung SDS for mild depression administrated as a structured interview. Cut off from 50 to 59.	At baseline: 18 (19%) 95% CI: 12.2 to 27.7 At 3 months: 11 (11%)	1

	Probable AD (NINCDS-ADRDA) Age: 77 (SD 6.7) Mean MMSE: 22.7 (SD 3, range 17-28) Mild to moderate AD at baseline			
Gilley et al. (2004)	Rush AD center outpatients USA N=410 at baseline N=360 follow up year 1, 313 year 2, 279 year 3, 188 year 4. Probable AD (NINCDS-ADRDA) Age: 75.5 (SD 7.3) Mean MMSE: from 18.7 (SD 4.3) at baseline to 7.1 (SD 5.1) at last evaluation Mild to moderate AD at baseline	HDRS (17 items) completed as a structured interview. No specific cut off point for MinD but ≥15 for depressive disturbances Definition of MinD based on DSM criteria	At year 1: 34 (9.4%) 95%CI: 6.8 to 12.9 At year 2: 40 (12.8%) At year 3: 39 (13.9%) At year 4: 17 (9.0%)	2

Note: AD: Alzheimer's Disease; **NINCDS-ADRDA:** National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria (McKhann et al. 1984); **DSM:** Diagnostic Statistical Manual of Mental Disorders; **SD:** Standard Deviation; **MMSE**: Mini Mental State Examination; **SCID:** Structured Clinical Interview for DSM; **CSDD:** Cornell Scale for Depression in Dementia; **HDRS:** Hamilton Rating Scale for Depression; **Zung SDS:** Zung Self-Rating Depression Scale; **MinD:** Minor Depressive disorder
*Data for MinD+AD group only †CI provided by authors
†† Note this study also investigated the association of MinD and different Apolipoprotein E (APOE) genotypes; there was no association between APOE genotype and MinD.

Table 3 Characteristics of study reporting incidence of MinD in Alzheimer's Disease

Study	Sample	Diagnostic criteria for MinD	Incidence at 1 year follow-up N(%)
Ballard et al. (1996)	Memory clinic outpatients UK N= 63 (36 without RDC for MinD or MD) Probable AD (NINCDS-ADRDA) Age: over 65-years	RDC for MinD based on CSDD	29.8% (95% CI: 18-46.9) developed RDC MinD

Note: RDC: Research Diagnostic Criteria**; MinD:** Minor Depression; **MD:** Major Depression; **NINCDS-ADRDA:** National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria; **CSDD:** Cornell Scale for Depression in Dementia

Table 4 Characteristics of studies reporting on treatments for MinD in Alzheimer's disease

Study	Sample	Diagnostic criteria for MinD	Intervention	Primary outcome	Results
Drye et al. (2011) DIADS-2 Study RCT	Memory clinic outpatients and Veteran geriatric clinics USA N = 131 MinD: 54 (41.2%) Probable AD (DSM-IV-TR and MMSE score of 10-26 inclusive) Age: Median 79 MMSE: 20 (IQR: 16-24) Mild to moderate AD	Diagnostic criteria of depression in AD (NIMH-dAD; Olin et al. 2002) and as operationalized by authors Meeting 3 or 4 of MaD (DSM-IV) depressive symptoms (including either anhedonia or dysphoria)	Sertraline (target dose 100mg/day) + standardized psychosocial intervention Placebo + standardized psychosocial intervention Over 24 weeks	AD – modified mADCS-CGIC CSDD	Sertraline not superior to placebo on mADCS-CGIC or CSDD scores at 12 or 24 weeks
Teri et al. (1997) RCT	Memory clinic outpatients USA N = 72 (caregiver dyads) MinD: 18 (45%)	RDC & DSM-III-R criteria for MinD HDRS ≥ 10	1. Behaviour therapy based on pleasant events 2. Behaviour therapy based on problem solving Over 9 weeks	HDRS CSDD BDI	Patients with MinD at baseline still met criteria for MinD at post-treatment (p values not reported) at 9 weeks No further data provided

	Probable AD (NINCDS-ADRDA) Age: 76.4 (SD 8.2) MMSE: 16.5 (SD 7.4) Moderate AD	Control group: waiting list		

Note: MinD: Minor Depression**; DSM:** Diagnostic Statistical Manual of Mental Disorders; **MMSE:** Mini Mental State Examination; **IQR**: Interquartile range; **NIMH-dAD:** National Institute of Mental Health, depression of Alzheimer's Disease criteria; **MaD:** Major depressive episode; **mADCS-CGIC:** modified Alzheimer's Disease Cooperative Study Clinical Global Impression of Change; **CSDD**: Cornell Scale for Depression in Dementia**; NINCDS-ADRDA:** National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; **SD:** Standard Deviation; **RDC:** Research Diagnostic Criteria**; HDRS:** Hamilton Depression Rating Scale; **BDI:** Beck Depression Inventory.

Table 5: Characteristics of studies reporting on neuroanatomical changes and genetic contribution of MinD in Alzheimer's Disease

Study	**Sample**	**Diagnostic criteria for MinD**	**Brain areas/genetic loci**	**Results**
Lebedeva et al. (2014) Cross-sectional study	Memory clinic outpatients Sweden (2 cohorts) N= 41 N=148 Subsyndromal depression group: N= 16 (39%) and N=84 (56.8%) Probable AD (NINCDS-ADRDA, DSMIV/ICD-10) Age: Median 66.0 (IQR 62.5 – 75) MMSE: 22 (range 20-26) Age: Median 76.0 (IQR 70.6 – 80.3) MMSE: 24 (range 23-25)	GDS-15 scores 1-5 CSDD 6 or more	Cortical thickness and CSF biomarkers	Subsyndromal depression was associated with thinning in the left temporal and inferior parietal regions, including supramarginal, superior and inferior temporal and fusiform gyri. In those with subsyndromal depression there was a negative correlation between CSF levels of the t-protein and cortical thickness, especially in the right posterior cingulate cortex and right parahippocampal and fusiform gyri.
Lee et al. (2014)	Recruited from Research dementia centres USA	Subsyndromal depression - DSM-IV criteria using SCID	Medial prefrontal regional gray matter volume	No significant differences between those with and without subsyndromal depression.

Cross-sectional study	N=27 Probable AD (NINCDS-ADRDA) Subsyndromal depression: 12 (71%) Age = 77.8 Mean = 22.3 (SD 4.4)	Medial prefrontal, and limbic regional gray matter volume, and lobar white matter lesions (WMLs)

NINCDS-ADRDA: National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria; **DSM:** Diagnostic Statistical Manual of Mental Disorders; **IQR**: Interquartile range; **MMSE:** Mini Mental State Examination; **GDS-15**: Geriatric Depression Scale; **CSDD**: Cornell Scale for Depression in Dementia; **SD:** Standard Deviation; **SCID:** Structured Clinical Interview for DSM.

Figure 2. Funnel plot to test publication bias of the 10 studies included in the meta-analysis

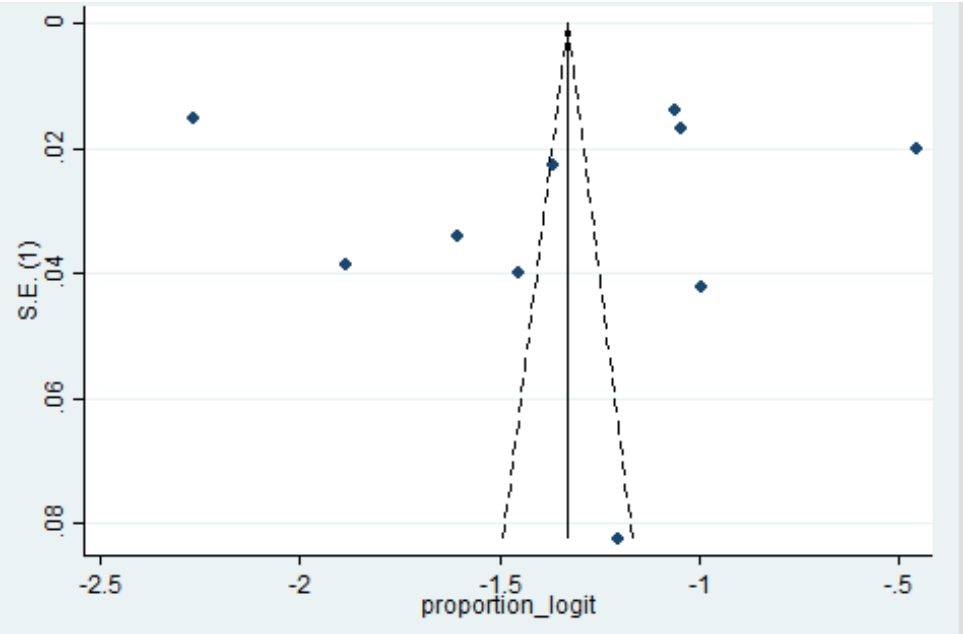

Table 6. Quality ratings of prevalence studies

	Sample	*Inclusion and exclusion criteria*	*Diagnosis*	*Statistical analysis*	*Number of high quality ratings for the study*
Cross-sectional studies					
Lee et al. (2016)	Moderate	High	High	Low	**2**
Starkstein et al. (2005)	Moderate	High	High	Low	**2**
Starkstein et al. (2011)	Moderate	High	High	Low	**2**
Hargrave et al. (2000)	Low	High	High	Low	**2**
Lyketsos et al. (1997a)	Moderate	Low	High	Low	**1**
Lyketsos et al. (1997b)	Moderate	High	Moderate	High	**2**
Vida et al. (1994)	Low	Moderate	High	Low	**1**
Li et al. (2001)	Moderate	Moderate	Moderate	Low	**0**
Longitudinal studies					
Mormont et al. (2014)	Moderate	High	Low	Low	**1**
Gilley et al. (2004)	High	High	Moderate	Low	**2**

Table 4. PRISMA 2009 Checklist

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.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4, 5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4,5
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.	N/A
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.	5, 6
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.	5, 6, 7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	1 (Appendix)
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).	5, 6, 7
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.	5, 6, 7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6-9
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.	6, 9, 25
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6-7

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.	6-7

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).	25
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8, 9
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.	7, 24, 2-3 (Appendix)
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.	4-9 (Appendix)
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).	11 (Appendix)
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.	8-9; (see Figures documents)
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8-9; (see Figures documents)
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	11 (Appendix)
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	8-9
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).	11-13
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).	14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14-15
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.	N/A