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Complete List of Authors:	Manea, Laura; University of York, Health Sciences Boehnke, Jan; University of York Gilbody, Simon; The University of York, Department of Health Sciences Moriarty, Andrew; University of York, Health Sciences McMillan, Dean; University of York, Department of Health Sciences
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Are there researcher allegiance effects in diagnostic validation studies of the PHQ-9? A systematic review and meta-analysis

Laura Manea MMedSci MRCPsych*, Jan Boehnke PhD, Simon Gilbody DPhil FRCPsych FRSA, Andrew Moriarty MSc, Dean McMillan PhD

*Corresponding Author

Hull York Medical School and Department of Health Sciences, ARRC Building, University of York, YO10 5DD

Email: laura.manea@york.ac.uk

Abstract

Objectives To investigate whether an authorship effect is found that leads to better performance in studies conducted by the original developers of the PHQ-9 (non-independent studies).

Design Systematic review with random effects bivariate diagnostic meta-analysis. Search strategies included electronic databases, examination of reference lists, and forward citation searches.

Inclusion criteria Included studies provided sufficient data to calculate the diagnostic accuracy of the PHQ-9 against a gold standard diagnosis of major depression using the algorithm or the summed item scoring method at cut-off point 10.

Data extraction Descriptive information, methodological quality criteria, and 2×2 contingency tables.

Results

Seven non-independent and twenty independent studies reported the diagnostic performance of the PHQ-9 using the algorithm scoring method. Pooled diagnostic odds ratio (DOR) for the first group was 64.40, and 15.05 for independent studies group. The allegiance status was a significant predictor of DOR variation ($p < 0.0001$).

Five non-independent studies and twenty-six independent studies reported the performance of the PHQ-9 at recommended cut-off point of 10. Pooled DOR for the non-independent group was 49.31, and 24.96 for the independent studies. The allegiance status was a significant predictor of DOR variation ($P = 0.015$).

Some potential alternative explanations for the observed authorship effect including differences in study characteristics and quality were found, though it is not clear how some of them account for the observed differences

Conclusions

Non-independent studies reported better performance of the PHQ-9. Allegiance status was predictive of variation in the DOR. Based on the observed differences between independent

and non-independent studies we were unable to conclude or exclude that allegiance effects are present in studies examining the diagnostic performance of the PHQ-9. This study highlights the need for future meta-analyses of diagnostic validation studies of psychological measures to evaluate the impact of researcher allegiance in the primary studies.

Strengths and limitations of this study

- An original study–the first meta-analysis of diagnostic validation studies of psychological measures to evaluate the impact of researcher allegiance.
- Using rigorous methodology–strict inclusion/exclusion and quality assessment criteria.
- We found that the allegiance effect was a significant predictor of the variation of the diagnostic odds ratio in the meta-regression analysis.
- Substantial variability observed in methodological quality of included studies.
- Based on the observed methodological differences between the independent and non-independent studies we were unable to conclude or exclude that allegiance effects are present in studies examining the diagnostic performance of the PHQ-9.

Research on allegiance effects has a long tradition in psychotherapy research. In this context *allegiance* describes the phenomenon that researchers and clinicians who developed a treatment approach or are for other reasons invested in it tend to find larger effect sizes in favour of their treatment than for comparison groups. (Luborsky et al., 2006) This finding has been extensively replicated (Dragioti, Dimoliatis, & Evangelou, 2015; Munder, Brütsch, Leonhart, Gerger, & Barth, 2013) and is also robust when the quality of research is controlled for. Researcher allegiance is subject of on-going debates about the design of efficacy studies as well as implications for policy. (Dragioti et al., 2015; McLeod, 2010; Winter, 2010) Researcher allegiance is also discussed widely in the literature on experimental as well as evaluation research. (Staines & Cleland, 2007) Since the motivational underpinnings of allegiance effects are potentially far more ingrained into human behaviour and decision making than previously thought (e.g., (Markman & Hirt, 2002)), they may occur commonly in clinical research in general.

Although it has been suggested that allegiance effects may play a role in the validation of psychological screening and case-finding tools (e.g., O'Shea et al., in press), systematic evaluations of this hypothesis are rare and studies that acknowledge potential allegiance effects in such studies mainly come from forensic psychology and psychiatry backgrounds. (Blair, Marcus, & Boccaccini, 2008; Lilienfeld & Jones, 2008; Singh, Grann, & Fazel, 2013; Walters, 2009) Diagnostic validation studies are geared at establishing the sensitivity and specificity of a screening or case finding tool, which is used in practice to differentiate cases from non-cases or to decide about whether further assessment or treatment is indicated or will be offered An allegiance effect in such studies would be seen in systematically higher sensitivities or specificities if the original author(s) is(are) part of the team of such a study. Such a bias would have a deleterious affect on practice through promising over-optimistic accuracy of the screening or case finding tool or in evaluating the cost-effectiveness of the measure in a screening or case-finding context.

The depression module of the Patient Health Questionnaire (PHQ-9) is a widely used depression-screening instrument in non-psychiatric settings. The PHQ-9 was developed by a team of researchers, with its development underwritten by an educational grant from Pfizer US Pharmaceuticals. (Kroenke, Spitzer, & Williams, 2001) The PHQ-9 can be scored using different methods, including an algorithm based on DSM-IV criteria and a cut-off based on summed-item scores. The psychometric properties of these two approaches have been summarised in two recently published meta-analyses. (Manea, Gilbody, & McMillan, 2015;

Moriarty, Gilbody, McMillan, & Manea, 2015)The goal of the current review is to investigate, based on an established database of PHQ-9 diagnostic validation studies (Manea et al., 2015; Moriarty et al., 2015), whether an allegiance effect is found that leads to an increased sensitivity and specificity in studies that were conducted by researchers closely connected to the original developers of the instrument.

METHODS

Study Selection

Similar search strategies were used in both systematic reviews. (For full details please see Manea et al. (2014) and Moriarty et al. (2015)). Embase, MEDLine and PSYCHInfo were searched from 1999 (when the PHQ-9 was first developed) to August 2013 (Manea et al., 2015) and September 2013 (Moriarty et al., 2015) respectively, using the terms "PHQ-9", "PHQ", "PHQ$" and "patient health questionnaire". The reference lists of studies fitting the inclusion criteria were manually searched and a reverse citation search in Web of Science was performed. Authors of unpublished studies were contacted and conference abstracts were reviewed in an attempt to minimise publication bias.

The following inclusion-exclusion criteria were used:

Population: Adult population. *Instrument:* Studies that used the PHQ-9. *Comparison (reference standard):* The accuracy of the PHQ-9 had to be assessed against a recognised gold-standard instrument for the diagnosis of either Diagnostic and Statistical Manual (DSM) or International Classification of Disease (ICD) criteria for major depression. Studies were included if the diagnoses were made using a standardised diagnostic structured interview schedule (e.g. Mini International Neuropsychiatric Interview (MINI), Structured Clinical Interview for DSM Disorders (SCID)). Unguided clinician diagnoses with no reference to a standard structured diagnostic schedule or comparisons of the PHQ-9 with other self-report measures were excluded. Studies were also excluded if the target diagnosis was not major depressive disorder (MDD, e.g. any depressive disorder). *Outcome:* Studies had to report sufficient information to calculate a 2*2 contingency table for the algorithm or the recommended cut-off point 10. *Study design:* Any design. *Additional criterion:* We avoided double counting of evidence by ensuring that only one study of those that reported overlapping datasets in different journals were included in the meta-analysis. Citations with

overlapping samples were examined to establish whether they contained information relevant to the research question that was not contained in the included report.

Quality assessment

Quality assessment was performed using the QUADAS-2 tool, a tool for evaluating the risk of bias and applicability of primary diagnostic accuracy studies when conducting diagnostic systematic reviews. (Whiting et al., 2011) It covers the areas of: patient selection, index test, reference standard and flow and timing. (Mann, Hewitt, & Gilbody, 2009) This tool was adapted for the two reviews and quality assessments were carried out by two independent reviewers for all studies included in the reviews.

Data synthesis and statistical analysis

We constructed 2x2 tables for cut-off point 10 (Moriarty et al., 2015) and the algorithm scoring method (Manea et al., 2015) Pooled estimates of sensitivity, specificity, positive/negative likelihood ratios, and diagnostic odds ratios were calculated using random effects bivariate meta-analysis. (Reitsma et al., 2005) Summary Receiver Operator Characteristic curves (sROC) were constructed using the bivariate model to produce a 95% confidence ellipse within ROC space. (Walter, 2002) Each data point in the summary ROC space represents a separate study, unlike a traditional ROC plot, which explores the effect of varying thresholds on sensitivity and specificity in a single study.

We undertook a meta-regression analysis of logit diagnostic odds ratio using research allegiance as covariate in the meta-regression model. (Lijmer, Bossuyt, & Heisterkamp, 2002; S. G. Thompson & Higgins, 2002) Analyses were conducted using STATA version 12, with the metan, metandi and metareg user-written commands.

Allegiance Rating

We rated authorship on a paper of any of the developers of the PHQ-9 - Kurt Kroenke, MD, Robert L Spitzer, MD, and Janet B W Williams – as an indicator of potential allegiance. We also rated as evidence of allegiance as acknowledged collaborations with the developers of the PHQ-9, even if they were not listed as co-authors or if the authors acknowledged funding from Pfizer to conduct the study.

RESULTS

Overview of included studies

31 studies reported the diagnostic properties of the PHQ-9 at cut-off point 10 and were included in this analysis (Moriarty et al., 2015) 27 studies were included in the algorithm review (Manea et al., 2015). The study selection flowcharts can be found in Appendix 1 (figures 1 and 2). The characteristics of these studies are reported in tables 1 and 2 and the results of the methodological assessment are presented in tables 3 and 4.

Algorithm scoring method

Descriptive characteristics

The descriptive characteristics of the included studies are presented in table 1. Seven individual studies that reported the diagnostic performance of the PHQ-9 using the algorithm scoring method were co-authored by the original developers of the PHQ-9 (Diez-Quevedo, Rangil, Sanchez-Planell, Kroenke, & Spitzer, n.d.; Gräfe, Zipfel, Herzog, & Löwe, 2004; Löwe et al., 2004; Spitzer, Kroenke, & Williams, 1999; Thekkumpurath et al., 2011), specifically acknowledged one of the developers and support by an educational grant from Pfizer US (Muramatsu et al., 2007), or were co-authored by the first author of a previous study that had also been co-authored by one of the developers (Navinés et al., 2012). Twenty independent studies reported the diagnostic properties of the PHQ-9 using the algorithm scoring method.

Three (43%, 3/7) of the non-independent studies were conducted exclusively in hospital settings (Diez-Quevedo et al., n.d.; Navinés et al., 2012; Thekkumpurath et al., 2011). The remaining four studies (67%, 4/7) were conducted in different settings or non-exclusively hospital settings: one in primary care (Spitzer et al., 1999) and three in mixed settings: psycho-somatic walk in clinics and family practices (Gräfe et al., 2004)[1], outpatient clinics

[1] This study provided separate estimates for the two settings in which it was conducted; therefore separate psychometric estimates were generated for each sample for both algorithm scoring method and summed items scoring method at cut-off point 10 (see below).

and family practices (Löwe et al., 2004) and primary care and hospital settings (Muramatsu et al., 2007). In the independent group, thirteen (65%, 13/20) studies were conducted in hospital settings (Eack, Greeno, & Lee, 2006; Fann et al., n.d.; Gelaye et al., 2013; Hyphantis et al., 2011; Inagaki et al.; Khamseh et al., 2011; Persoons, Luyckx, Desloovere, Vandenberghe, & Fischler, n.d.; Picardi et al., 2005; Stafford, Berk, & Jackson, 2007; Thombs, Ziegelstein, & Whooley, 2008; A. W. Thompson et al., 2011; Turner et al., 2012; van Steenbergen-Weijenburg et al., 2010). Of the remaining seven studies, six were conducted in primary care settings (Arroll et al., 2010; Ayalon, Goldfracht, & Bech, 2010; Henkel et al., 2004; Lamers et al., 2008; Lotrakul, Sumrithe, & Saipanish, 2008; Zuithoff et al., 2010) and one in a community sample (Gjerdingen, Crow, McGovern, Miner, & Center, 2009).

In both groups (independent and non-independent studies), the majority of studies validated a translated version of the PHQ-9. Two of the studies authored by developers (28%, 2/7) (Spitzer et al., 1999; Thekkumpurath et al., 2011), and eight (40%, 8/20) independent studies (Arroll et al., 2010; Eack et al., 2006; Fann et al., n.d.; Gjerdingen et al., 2009; Stafford et al., 2007; Thombs et al., 2008; A. W. Thompson et al., 2011; Turner et al., 2012) were conducted in English.

The mean prevalence of major depressive disorder in the group of studies co-authored by PHQ-9 developers was 13.4 (range 6.1% - 29.2%); in the independent group it was 15.5% (range 3.9% - 32.4%). The mean age of patients in the PHQ-9 developers group was 45.75; all but one study had a mean age in the range of 40 to 50 years. In the independent group the mean age was 54.6 (range 29.3 – 75.0), with almost half (8) of the studies reporting a mean age of over 60. The percentage of females in the PHQ-9 developers was 56.8% (range 28.6% - 67.8%) and in the independent group was 59.1 (18% -100%).

All of the non-independent studies used a self-reported PHQ-9, whereas in 7 independent studies (30%, 6/20) the PHQ-9 was administered by a researcher (Ayalon et al., 2010; Fann et al., n.d.; Gelaye et al., 2013; Gjerdingen et al., 2009; Hyphantis et al., 2011; Inagaki et al.). Apart from Muramatsu et al. (2007) all of the non-independent studies used the SCID as a gold standard; the independent studies used a wider range of gold standards including SCAN, CIDI, MINI, and C-DIS, though the SCID was also frequently used by the independent studies as well (45%, 9/20 studies).

Four out of the seven non-independent studies (57%) did not include a conflict of interests statement (Diez-Quevedo et al., n.d.; Gräfe et al., 2004; Muramatsu et al., 2007; Spitzer et al., 1999). Also, four (57%) of the non-independent studies acknowledged funding from Pfizer (Gräfe et al., 2004; Löwe et al., 2004; Muramatsu et al., 2007; Spitzer et al., 1999). Only one study (Muramatsu et al., 2007) acknowledged the collaboration with one of the developers of the PHQ-9.

Of the independent studies, twelve (60%) did not include a conflict of interests statement (Eack et al., 2006; Fann et al., n.d.; Gelaye et al., 2013; Gjerdingen et al., 2009; Henkel et al., n.d.; Hyphantis et al., 2011; Lamers et al., 2008; Lotrakul et al., 2008; Persoons et al., n.d.; Picardi et al., 2005; Stafford et al., 2007; A. W. Thompson et al., 2011). It appears that newer studies were more likely to include a conflict of interest statement, which may reflect a recent change in reporting. Funding was acknowledged by most studies (18/20) and most received funding from academic or/and health research institutions. Two studies received funding from pharmaceutical companies – Lundbeck (Ayalon et al., 2010) and Pfizer (Persoons et al., n.d.) and one study acknowledged that Pfizer Italia provided the Italian version of PHQ-9 and gave the authors permission to use it (Picardi et al., 2005).

Diagnostic test accuracy

Pooled sensitivity and specificity was calculated separately for the independent and non-independent studies. Pooled sensitivity for the non-independent studies of the PHQ-9 was 0.77 (95% CI = 0.70 – 0.84), pooled specificity was 0.94 (95% CI = 0.90 – 0.97) and the pooled diagnostic odds ratio was 64.40 (95% CI = 34.15 – 121.43). Heterogeneity was high (I^2 = 78.9%). Figure 1 represents the summary ROCs for this set of studies.

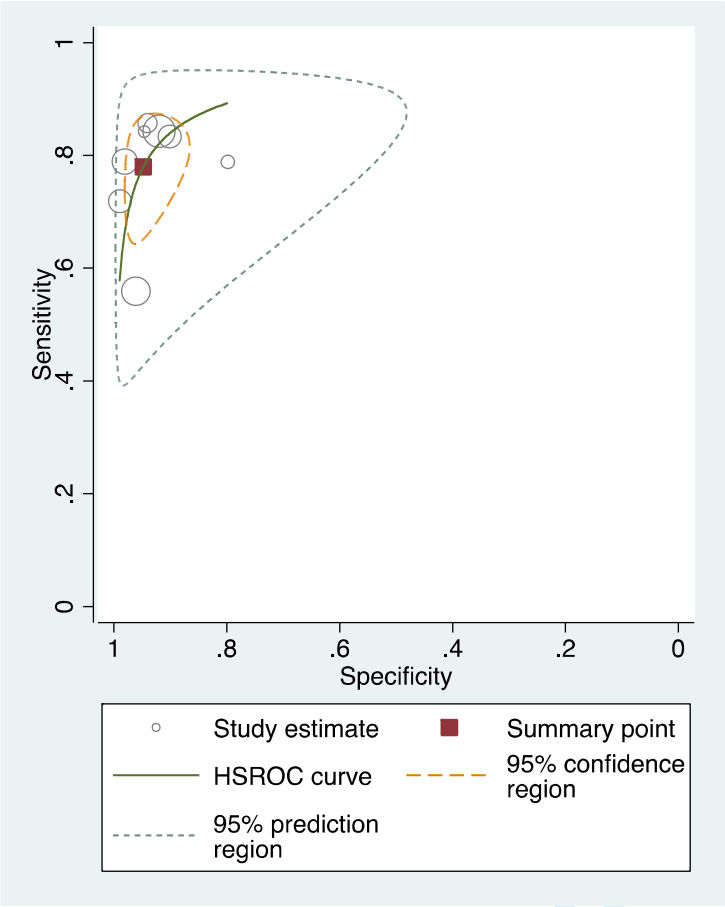

Figure 1. PHQ-9 algorithm scoring method summary ROC plot of diagnosis of major depressive disorder in non-independent studies. Pooled sensitivity and specificity using a bi-variate meta-analysis.

Pooled sensitivity for the independent studies was lower compared to the developer authored studies group at 0.48 (95% CI = 0.41 – 0.91); whereas pooled specificity was the same at 0.94 (95% CI = 0.91 – 0.95). The pooled diagnostic odds ratio was approximately four times lower at 15.05 (95% CI = 11.03 – 20.52) (see figure 2 or sROC). Heterogeneity was substantial at I^2 = 68.1 %.

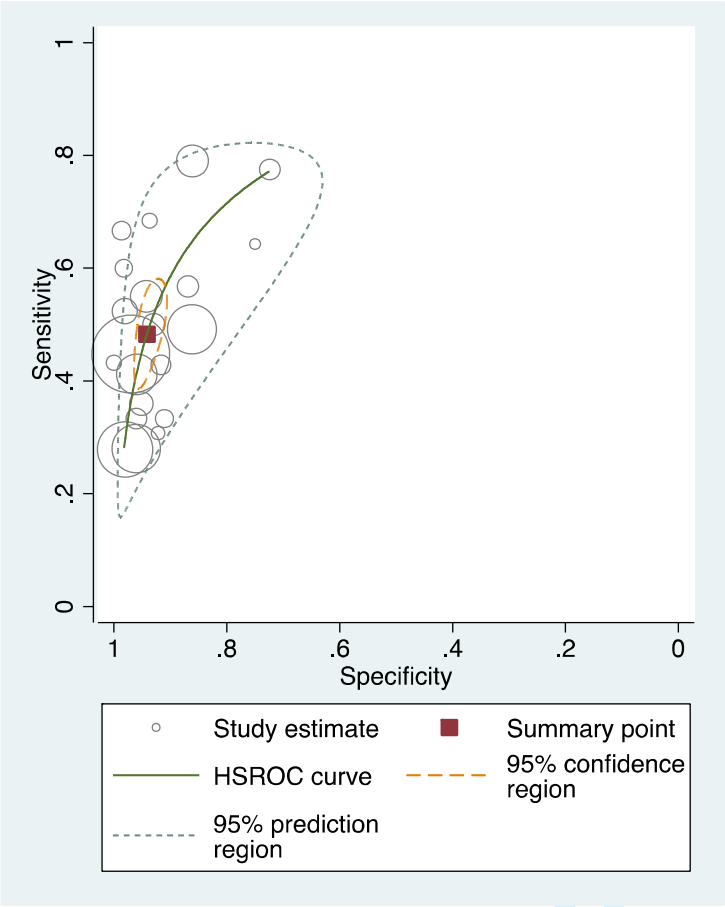

Figure 2. PHQ-9 algorithm scoring method summary ROC plot of diagnosis of major depressive disorder in independent studies. Pooled sensitivity and specificity using a bi-variate meta-analysis.

The meta-regression analysis for algorithm studies with independent status as the predictor of the diagnostic odds ratio showed that independent status was a significant predictor of the diagnostic odds ratio ($p < 0.0001$) and explained a substantial amount of the observed heterogeneity (51.54%).

Quality assessment

The results of the quality assessment using QUADAS-2 are given in table 3 for the studies reporting on the diagnostic performance of the algorithm scoring method. In the patient selection domain, more of the independent studies (65%, 13/20) than the non-independent (29%, 2/7) met the criterion for consecutive referrals. There were no marked differences on the other two criteria in this domain (avoid case-control design, avoid inappropriate exclusions). In the index test domain, the proportion of studies reporting that the PHQ-9 was conducted blind to the reference test was comparable between the two groups. There were differences in this domain for those studies using a translated version of the test. All non-English non-independent studies (5/5) used an appropriately translated version of the PHQ-9; whereas just over a half of the independent studies reported this (55%, 6/11). However, the majority of both sets of studies did not report details of psychometric properties of the translated version. For the reference test domain, nearly all studies in both groups were rated as using a reference test that would correctly classify the condition. While most studies conducted by the developers of the PHQ-9 reported that the reference test was interpreted blind to the PHQ-9 score (86%, 6/7), this was reported in only 60% (12/20) of the independent studies.

The two sets of studies that used translated versions of the reference test were broadly comparable. There was a slight indication that the non-independent studies were more likely to use an appropriately translated version of the reference test and report data on the psychometric properties of the translated version, though the numbers for the translated comparison are very low. There were, however, some more notable differences on the flow and timing domain. Most of the studies conducted by the developers ensured that the time between the index and reference test was under two weeks (86%, 6/7) in comparison to 70% (14/20) of the independent studies. More non-independent studies met the criterion for 'all participants included in the analysis' (57%, 4/7) than the independent studies (25%).

Summed items scoring method (cut-off point 10)

Descriptive characteristics

Table 2 presents the sample characteristics of the thirty-one PHQ-9 validation studies that reported the psychometric properties of the PHQ-9 at cut-off point 10. Five of these studies

were co-authored by the original developers of the instrument or acknowledged collaboration (Gräfe et al., 2004; Kroenke et al., 2001; Thekkumpurath et al., 2011; Williams et al., 2005) or were co-authored by the first author of a previous study that had also been co-authored by one of the developers (Navinés et al., 2012). Twenty-six studies were conducted by independent researchers.

Three (60%, 3/5) of the non-independent studies (Navinés et al., 2012; Thekkumpurath et al., 2011; Williams et al., 2005) and eleven independent studies (42%, 11/26) (Chagas et al., 2013; Elderon, Smolderen, Na, & Whooley, 2011; Fann et al., n.d.; Gelaye et al., 2013; Hyphantis et al., 2011; Khamseh et al., 2011; Rooney et al., 2013; Stafford et al., 2007; Thombs et al., 2008; Watnick, Wang, Demadura, & Ganzini, 2005; Zhang et al., 2013) were conducted in hospital settings.

Three (60%, 3/5) non-independent studies(Kroenke et al., 2001; Thekkumpurath et al., 2011; Williams et al., 2005) and thirteen independent studies (13/26) (Adewuya, Ola, & Afolabi, 2006; Arroll et al., 2010; Elderon et al., 2011; Fann et al., n.d.; Fine et al., 2013; Gilbody, Richards, Brealey, & Hewitt, 2007; Gjerdingen et al., 2009; Phelan et al., 2010; Rooney et al., 2013; Sidebottom, Harrison, Godecker, & Kim, 2012; Stafford et al., 2007; Thombs et al., 2008; Watnick et al., 2005), were conducted in English.

The mean prevalence of major depressive disorder in the group of studies authored by PHQ-9 developers was 13.2% (range 6.1% - 33.5%) and in the independent group was 16.1% (range 2.5% - 43.2%). The mean age of patients in the PHQ-9 developers group studies was 48.1 (range 41.9 -61.0) and in the 26 independent studies that reported these data was 49.1 (range 23.0 – 78.0). The percentage of females in the PHQ-9 developers studies that reported these data(Gräfe et al., 2004; Kroenke et al., 2001; Navinés et al., 2012; Thekkumpurath et al., 2011) was 56.3% (range 28.6% – 67.8%) and in the independent group was 64.9 % (range 12% -100%).

Three of the non-independent studies used the self-reported mode of administration and two of them did not specify how the PHQ-9 was administered. In 9 independent studies (34%, 9/26) the PHQ-9 was administered by the researcher (de Lima Osório, Vilela Mendes, Crippa, & Loureiro, 2009; Fann et al., n.d.; Fine et al., 2013; Gelaye et al., 2013; Gjerdingen et al., 2009; Hyphantis et al., 2011; Patel et al., 2008; Phelan et al., 2010; Sidebottom et al., 2012). All studies authored by developers used SCID as a gold standard; the independent studies used a wider range of gold standards including SCAN, CIDI, MINI, CIS-R, C-DIS, though the SCID was used in half of the studies (50%, 13/26 studies).

Three non-independent studies (60%) did not include a conflict of interests statement (Gräfe et al., 2004; Kroenke et al., 2001; Williams et al., 2005). Two of these studies (Gräfe et al., 2004; Kroenke et al., 2001) acknowledged funding from Pfizer. None of the non-independent studies acknowledged collaboration or authorship of one of the developers of the PHQ-9.

Of the independent studies, thirteen (42%) did not include a conflict of interests statement (Adewuya et al., 2006; Arroll et al., 2010; Azah et al., 2005; de Lima Osório et al., 2009; Fann et al., n.d.; Gelaye et al., 2013; Gjerdingen et al., 2009; Hyphantis et al., 2011; Liu et al., 2011; Lotrakul et al., 2008; Stafford et al., 2007; Watnick et al., 2005; Wittkampf et al., 2009). Similar to the algorithm studies, the newer studies were more likely to include a conflict of interest statement. Funding was acknowledged by most studies (27/31) and most received funding from academic or/and health research institutions. One study (Gilbody et al., 2007) acknowledged that the last author involved in the development of one of the instruments (CORE-OM), 'but does not gain financially from its use'. One study (Elderon et al., 2011) acknowledged funding from industry, AHA Pharmaceuticals Roundtable, but stated that 'the funding organisations had no role in the design or conduct of the study, collection, management, analysis or interpretation of data; or preparation, review or approval of the manuscript. Fine et al., 2013 disclosed that the last author had financial and consulting interests (Pfizer was not cited as one of them).

Diagnostic test accuracy

Pooled sensitivity for the studies linked to the developers of the PHQ-9 was 0.87 (95% CI = 0.77 – 0.93), pooled specificity was 0.87 (95% CI = 0.76 – 0.94) and the pooled diagnostic odds ratio was 49.31 (95% CI = 25.74 – 94.48) – see table 5. Heterogeneity was moderate (I^2 = 55.1%). Figure 4 represents the summary ROCs for this group.

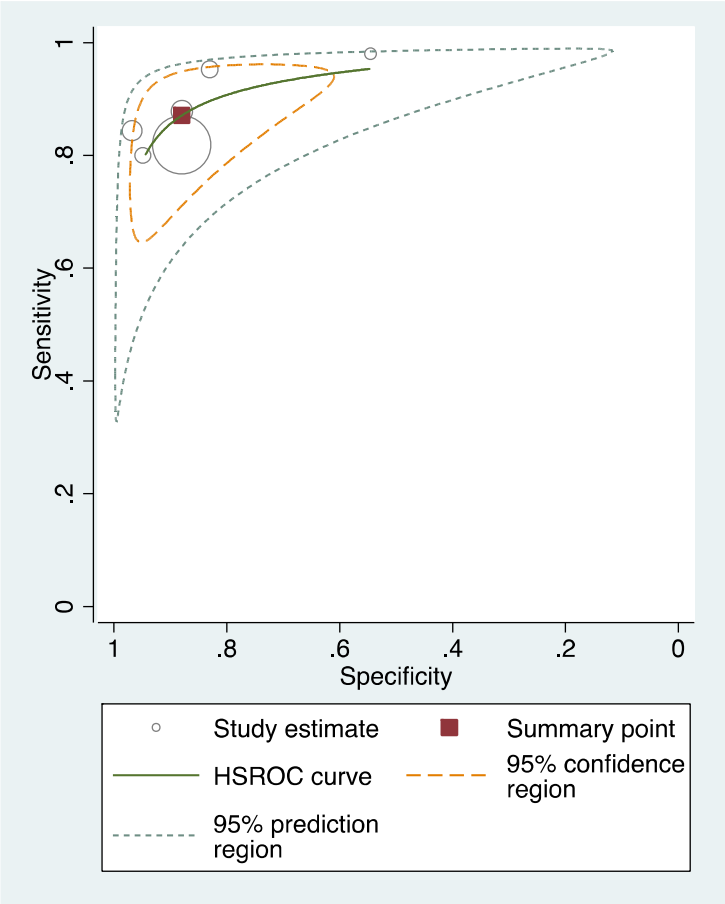

Figure 3. PHQ-9 summed items scoring method at cut-off point 10 summary ROC plot of diagnosis of major depressive disorder in non-idependent studies. Pooled sensitivity and specificity using a bi-variate meta-analysis.

Pooled sensitivity for the independent studies was 0.76 (95% CI, 0.67 – 0.83), pooled specificity was 0.88 95% CI (0.85 – 0.91) and the pooled diagnostic odds ratio was 24.96 (95% CI 14.81 – 42.08), approximately half that of the non-independent studies (table 5). Heterogeneity was high at $I^2 = 81.5$ %. Figure 5 represents the summary ROCs for this group.

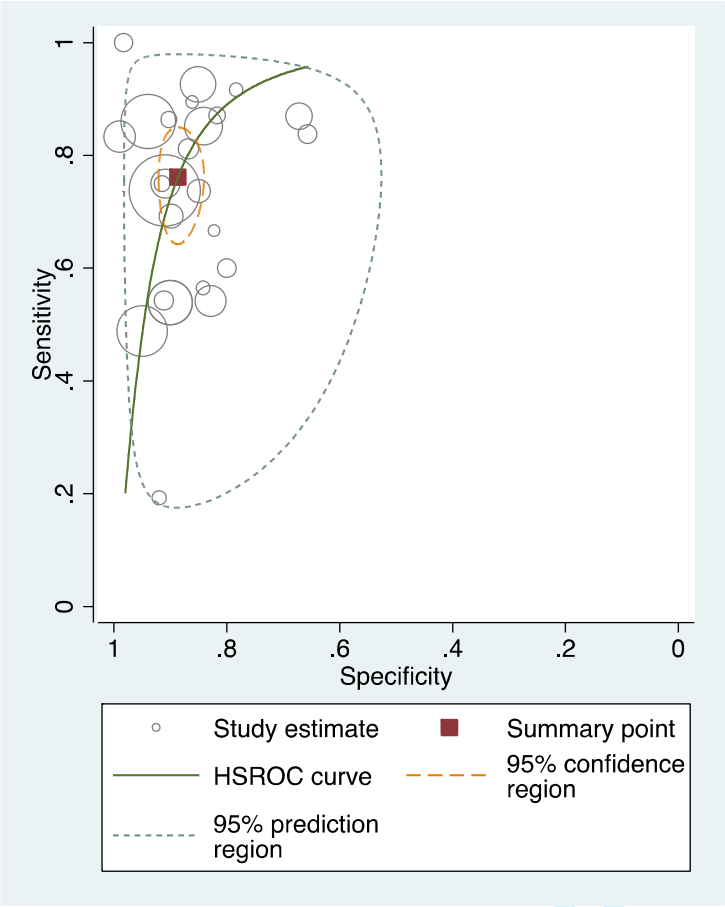

Figure 4. PHQ-9 summed items scoring method at cut-off point 10 summary ROC plot of diagnosis of major depressive disorder in independent studies. Pooled sensitivity and specificity using a bi-variate meta-analysis.

The meta-regression for the studies using a cut-off point of 10 with allegiance status of the predictor showed that allegiance status was a significant predictor of the diagnostic odds ratio (P = 0.015) and explained 18.95% of observed heterogeneity.

Quality assessment

The results of the quality assessment using the QUADAS-2 are given in table 4. For the patient selection domain, the two groups of studies were broadly comparable on two items (consecutive or random sample, avoid case-control design). However, all of the studies from the non-independent studies were rated as avoiding inappropriate exclusions (5/5) in contrast to 58% (15/26) of the independent studies.

On the index test domain, there were a number of differences between the two groups of studies. More of the independent studies (81%, 21/26) reported that the PHQ-9 was interpreted blind to the reference test compared to 60% (3/5) of the studies conducted by the developers of the PHQ-9. All (5/5) of the studies from the PHQ-9 developers were rated as pre-specifying the threshold on the PHQ-9 compared to 73% (19/26) of the independent studies. The two sets of studies were broadly comparable in terms of two items from the reference test domain (correctly classify target condition, reference test interpreted blind). Only one of the studies from the developers of the PHQ-9 used a translated version of the index test or reference test, so it is not possible to comment on differences between the two sets of studies in terms of these items from the index or reference test domains. For the flow and timing domain, the two groups of studies were broadly comparable for two of the criteria (interval of two weeks or less, all participants receive same reference test). However, fewer than half of the independent studies met the criterion for 'all participants included in the analysis' (42%, 11/26); whereas all of the studies by the developers of the PHQ-9 met this criterion.

Discussion

This is to our knowledge the first systematic examination of a possible 'allegiance' or authorship effect in the validation of screening or case finding psychological instrument for a

common mental health disorder. We reviewed diagnostic validation studies of the PHQ-9, a widely used depression screening-instrument. We found that non-independent studies reported higher sensitivity paired with similar specificity compared to studies conducted by independent researchers. When entered as a covariate in meta-regression analyses, independence status was predictive of variation in the DOR for both the algorithm scoring method and the summed-item scoring method at a cut-off point of 10.

Previous research has proposed several possible explanations for the allegiance effect (Blair et al., 2008; Lilienfeld & Jones, 2008; Singh et al., 2013). One possibility is the advertent bias that may serve to inflate the performance of a test when evaluated by those who have developed it. However, before concluding that the differences are due to this, it is important to explore and rule out alternative explanations. First, it is possible that any observed differences are a result of differences in study characteristics of the two sets of studies (e.g., setting, clinical population). Secondly, differences in the methodological quality of the studies may also account for any differences. These possibilities are examined below.

Difference in study characteristics as potential alternative explanations

The two sets of studies were broadly comparable in terms of gender and the prevalence of depression, so these variables are unlikely to offer an explanation for the differences. While there were some indications from both sets of comparisons that the PHQ-9 may have been researcher-administered more often in the independent studies, it is not immediately clear how this would lead to lowered diagnostic performance.

The diagnostic meta-analyses of the PHQ-9 (Manea et al., 2015; Moriarty et al., 2015) have shown that the sensitivity and DOR of the PHQ-9 tends to be lower in hospital settings for both algorithm and summed-item scoring methods. Whilst the fact that proportionally more independent algorithm studies were conducted in secondary care could explain the lower sensitivity and DOR values in the algorithm studies, in the studies that reported the cut-off point of 10 this would not be the case as proportionally more studies authored by developers were conducted in hospital settings.

Similarly, differences in the proportions of studies using translated versions of the PHQ-9 are also unlikely to offer an obvious explanation of the difference in diagnostic performance, because in the algorithm set of studies more of the non-independent studies used a translated version of the test, but the proportions were in the opposite direction for the studies using a cut off of 10. A similar conclusion is also likely to apply to the age of the samples. There were more older adults studies in the independent than non-independent studies in the algorithm comparison. Depression could be more difficult to identify in older adults due to physical co-morbidities that may present with similar symptomatology to depression and could account for the lower diagnostic performance in the independent studies. However, the independent samples in the studies that reported the psychometric properties at cut-off point 10 had younger samples than the non-independent studies, so this would not support this interpretation.

The SCID was used as the gold standard in nearly all of the non-independent studies. The fact that some independent studies used other gold standards could potentially explain the poorer psychometric properties of the PHQ-9 in these studies. The SCID is often regarded as the most valid of the available semi-structured interviews used in depression diagnostic validity studies as the reference standard. If we assume that this is the case and, furthermore, that the PHQ-9 is an accurate method of screening for depression, then the PHQ-9 may be more likely to agree with the SCID than other reference standards.

Differences in methodological quality as potential alternative explanations

The quality of the studies was evaluated using the QUADAS-2. Although there were several potential methodological differences between the two groups of studies from the algorithm papers, not all of these offer obvious explanations of the observed differences and some are unlikely as explanations. For example, more of the studies from the developers of the PHQ-9 ensured that the reference test was interpreted blind to the index test. This is unlikely to account for the observed differences, because a lack of blinding is typically associated with artificially increased diagnostic performance, which is in the opposite direction to the pattern of results observed here. The impact of some other differences is less clear-cut. For example,

a higher number of the independent studies met the criterion for consecutive referrals. For this to provide an explanation of the of the observed differences, the non-consecutive nature of the referrals in the studies by those who had developed the PHQ-9 would need to have led to the over-inclusion of true positives or under-inclusion of false negatives given that these studies tended to report higher sensitivity relative to the independent studies (and vice versa for the independent studies). It is not immediately obvious how this would occur. The studies by the developers of the PHQ-9 were more likely to have met the criterion of 'included all participants in the analysis'. It is possible that the greater loss of participants from the independent studies may have artificially reduced the observed diagnostic accuracy, though, again, it is not immediately obvious how this would have affected the true positive and false negative rates. Although there is not an obvious explanation of how these differences in methodological quality could account for the observed differences in diagnostic performance, it is important to recognise that they cannot on that basis be ruled out.

There are, however, two differences in methodological quality among the algorithm studies that are clearer potential alternative explanations. The higher rate of appropriate translations among the studies conducted by the developers of the PHQ-9 is potentially important, because lower diagnostic estimates may be expected from studies that have poorly translated versions of the index test. In the flow and timing domain, more of the studies by the developers of the PHQ-9 ensured that there was a less than two-week interval between the index and reference test. This is consistent with lower diagnostic performance in the independent studies: as the interval increases it is likely that depression status may change and this would lead to lower levels of agreement between the index test and the reference test.

There were also differences on some quality assessment items between the two sets of studies in the summed item scoring method comparison. The threshold was reported as pre-specified in all of the studies by the developers of the PHQ-9 in contrast to approximately three quarters of the independent studies. On the face of it, this is unlikely to explain the observed differences, because the use of a pre-specified cut-off point is likely to be associated with lower not higher diagnostic test performance. One possibility, however, is that studies that performed poorly at this cut-off point were less likely to be reported by those who had

developed the measure. As discussed in more detail in the limitations section, we were unable to explore this possibility through the use of formal tests for publication bias.

All non-independent studies avoided inappropriate exclusions compared to approximately half of the independent studies. While this is a potential alternative explanation of the differences it is not immediately obvious how this would explain the differences in diagnostic performance between the two sets of studies. Fewer than half of the independent studies met the criterion for 'all participants included in the analysis' in contrast to all of the studies by the developers of the PHQ-9 met this criterion, but again this difference should if at usually work against the inclusive studies, not those excluding cases. More of the independent studies reported that the PHQ-9 was interpreted blind to the reference test. This does offer a potential explanation, because the absence of blinding may artificially inflate diagnostic accuracy.

Limitations

The results of this review need to be viewed in the light of the limitations of the primary studies that contributed to the review and the review itself. An important consideration is to establish whether any observed differences between the diagnostic performance of the independent and non-independent studies are better accounted for by study characteristic or methodological differences. Caution, however, is needed in interpreting any differences, because of the small number of non-independent studies in both the algorithm and cut-off 10 comparisons. The small number of non-independent studies also meant that we were also unable to explore the potential role of publication bias in the independent and non-independent studies. At least 10 studies are required to use standard methods of examining publication bias, but the number of non-independent studies in both the algorithm and cut-off 10 comparisons were fewer than this.

Conclusions and implications for further research.

The aims of the review was to investigate whether an allegiance effect is found that leads to an increased diagnostic performance in diagnostic validation studies that were conducted by teams connected to the original developers of the PHQ-9. Our analyses showed that diagnostic studies conducted by independent researchers had lower sensitivity paired with similar specificity compared to studies that were classified as non-independent. This conclusion held for both the algorithm and cut-off 10 studies. We explored a range of possible alternative explanations for the observed allegiance effect including both differences in study characteristics and study quality. A number of potential differences were found, though for some of these it is not clear how they would necessarily account for the observed differences. However, there were a number of differences that offered potential alternative explanations unconnected to allegiance effects. These included the greater use of the SCID in the studies rated as non-independent in both the algorithm and the cut-off 10 studies. In the algorithm studies, the studies rated as non-independent were also more likely to use an appropriate translation of the PHQ-9 and were also more likely to ensure that the index and reference test were conducted within two weeks of each other, both of which may be associated with an improvement in observed diagnostic performance of an instrument. The majority of studies in both meta-analyses did not provide clear statements about potential conflict of interest and/or funding, however the newer studies were more likely to provide such statements, which may reflect increasing transparency in this area of research.

We cannot, therefore, conclude that allegiance effects are present in studies examining the diagnostic performance of the PHQ-9; but nor can we rule them out. Conflicts of interest are an important area of investigation in medical and behavioural research, particularly due to concerns about trial results being influenced by industry sponsorship. Future diagnostic validity in this area should as a matter of routine present clear statements about potential conflicts of interest and funding, particularly relating to the development of the instrument under evaluation. Future meta-analyses of diagnostic validation studies of psychological measures should routinely evaluate the impact of researcher allegiance in the primary studies examined in the meta-analysis.

Contributors LM led on all stages of the review and is the guarantor. We used an established database of diagnostic validation studies of the PHQ-9 (Manea et al., 2015; Moriarty et al., 2015) SG provided expert advice on methodology and approaches to assessment of the evidence base. AM carried out the literature searches, screened the studies, extracted data and assessed the quality of the included studies for one of the systematic reviews (Moriarty et al., 2015) . LM carried out the literature searches, screened the studies, extracted data and assessed the quality of the included studies for the other systematic review (Manea et al., 2015), analysed the data for both systematic reviews and drafted the report. JB involved in the development of the study, wrote the introduction section of the review and contributed to the production of the final report. DM supervised the quality assessment, methodology and approaches to evidence synthesis, provided senior advice and support throughout and contributed to the production of the final report. All parties were involved in drafting and/or commenting on the report.

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Table 1: Descriptive characteristics of algorithm studies (Manea et al., 2014)

Study	Sample characteristics (Country, setting, age, sex)	Sample size and % depressed	PHQ-9 characteristics	Diagnostic standard	a) Conflict of interest (COI) declaration b) Funding c) Relationship with original developers
Diez-Quevedo et al. (2001)	Country: Spain Setting: Medical and surgical tertiary hospitals Age (yrs): M=43 (SD=14.2) Female: 45.6%	N = 1003 Depressed: 8.2%	Administration: Self-report Language: Spanish	DSM-III-R SCID	a) a) No COI declaration b) Funding acknowledged (academic institutions) c) Not acknowledged
Gräfe et al. (2004)	Country: Germany	N = 528	Language: German	DSM-IV	a) No COI declaration b) Acknowledged funding from Pfizer c) Not acknowledged

	Setting: psychosomatic walk-in clinics and family practices Age (yrs): M = 41.9 (SD = 13.8) Female: 67.8%	Depressed: 29.2% psychosomatic patients; 6.16% medical patients	Administration: self-report	SCID	
Lowe et al. (2004)	Country: Germany Setting: Outpatient clinics and family practices	N = 501 Depressed: 13.2%	Administration: Self-report Language: German	DSM–IV SCID	a) COI declaration 'This study was supported by unrestricted restricted grants from Pfizer Germany and from the medical faculty of the University of Heidelberg Germany, and there are no COI.' b) Acknowledged funding from Pfizer and academic institution c) Not acknowledged

	Age (yrs): M = 41.7 (SD = 13.8) Female: 67.1%				
Muramatsu et al. (2007)	Country: Japan Setting: Primary care and general hospital Age (yrs): M = 43.3 (SD = 16.4) Female: 59.5%	N = 131 Depressed: 28.2%	Administration: Self-report Language: Japanese	DSM–IV MINI	a) No COI declaration b) Acknowledged funding from Pfizer c) Acknowledged one of the developers of the PHQ-9: 'The authors acknowledge Dr R L Spitzer'
Navinés et al. (2012)	Country: Spain	N = 500	Administration: Self-report	DSM–IV	a) All authors declared that they had no COI. b) Role of funding source declared c) Not acknowledged

	Setting: General hospital (patients with chronic HCV) Age (yrs): M = 43.4 (SD = 10.2) Female: 28.6%	Depressed: 6.4%	Language: Spanish	SCID	
Spitzer et al. (1999)	Country: US Setting: Primary care Age (yrs): M = 46 (SD = 17.2) Female: 66%	N = 3000 (585 received SCID) Depressed: 10%	Administration: Self-report Language: English	DSM-III-R SCID	a) No COI declaration b) Acknowledged funding from Pfizer. 'Drs Spitzer and Williams receive honoraria and consulting money from Pfizer Inc, which has supported this work.' c) N/A

Thekkumpurath et al. (2010)	Country: UK Setting: Hospital (cancer patients) Age (yrs): M = 61 Female: 63%	N = 782 Depressed: 6.3% (of the whole sample)	Administration: Not stated Language: English	DSM-IV SCID	a) COI declaration: 'Supported by Cancer Research UK' b) As in a) c) Not acknowledged
Ayalon et al. (2010)	Country: Israel	N = 153	Administration: Researcher administered	DSM-IV	a) COI declaration: 'The project was funded by an Investigator's Initiated Research Grant from Lundbeck International given to Dr Liat Ayalon. Lundbeck International had no other involvement in the project concept of design or in this paper. Per Bech has occasionally over the past 3 years until August 2008 received funding from and has been speaker or member of advisory boards for pharmaceutical companies with an interest in the drug treatment of affective disorders (Astra-Zeneca, Lilly, H. Lundbeck A/S, Lundbeck Foundation and Organon). ' b) Acknowledged funding from Lundbeck International

	Age (yrs): M = 75 (SD = 8.1) Female: 40.5 %	Depressed: 3.9 %	Language: Hebrew	SCID	
Eack et al. (2006)	Country: US Setting: Community mental health centers for children Age (yrs): M = 39.20 (SD 9.63) Female: 100%	N = 50	Administration: Self-report	DSM-IV	a) No COI declaration b) Funding acknowledged (academic /health research institutions)
Fann et al. (2005)	Country: US	Depressed: 28%	Language: English	SCID	
		N = 135	Administration: Telephone-administered	DSM-IV	a) No COI declaration b) Funding acknowledged (academic institutions)

	Setting: Trauma hospital (inpatients with traumatic brain injury) Age (yrs): M = 42 (SD=17.9) Female: 29.1%	Depressed: 16.3%	Language: English	SCID	
Gelaye et al. (2011)	Country: Ethiopia Setting: General hospital Age (yrs): 34.9 (SD=11.6) Female: 63.1 %	N = 363 Depressed: 12.6%	Administration: Researcher-administered Language: Amharic	DSM-IV SCAN	a) No COI declaration b) Funding acknowledged (academic /health research institutions)

Gjerdingen et al. (2009)	Country: US Setting: Community Age (yrs): M = 29.3 Female: 100%	N = 438 Depressed: 4.6%	Administration: Telephone or self-report Language: English	DSM-IV SCID	a) No COI declaration b) Funding acknowledged (academic /health research institutions)
Henkel et al. (2004)	Country: Germany Setting: primary care Age (yrs): not reported Female: 74%	N = 448 Depressed: 10%	Administration: self-report Language: German	DSM-IV CIDI	a) No COI declaration b) Funding acknowledged (academic /health research institutions)

Hyphantis et al. (2011)	Country: Greece Setting: Hospital – rheumatology patients Age (yrs): M = 54.2 (SD = 13.5) Female: 74%	N = 213 Depressed: 32.4%	Administration: Researcher administered Language: Greek	DSM-IV MINI	a) No COI declaration b) No funding acknowledgement
Inagaki et al. (2013)	Country: Japan Setting: General hospital Age whole sample (yrs): M = 73.5 (SD = 12.3)	N = 104 out of 511 received MINI Depressed: 7.4%	Administration: Researcher administered Language: Japanese	DSM-IV MINI	a) COI declaration: 'The authors declare that they have no competing interests.' b) Funding acknowledged (academic /health research institutions)

	Female: 59.3%				
Khamseh et al. (2011)	Country: Iran Setting: Diabetes clinic Age (yrs): M = 56.17 (SD = 9.60) Female: 51.9%	N = 185 Depressed: 43.2%	Administration: Self report Language: Persian	DSM-IV SCID	a) COI declaration: The authors declared no competing interests b) Funding acknowledged (academic /health research institutions)
Lamers et al. (2008)	Country: Netherlands Setting: Primary care (elderly) Age (yrs): M = 71.4 (SD = 6.90) Female: 48.2%	N = 713 Depressed: 10.7%	Administration: Self report Language: Dutch	DSM-IV MINI	a) No COI declaration b) Funding acknowledged (academic /health research institutions)

Lotrakul et al. (2008)	Country: Thailand Setting: Primary care Age (yrs): M = 45.0 (SD = 14.30) Female: 73.7%	N = 279 Depressed: 6.8%	Administration: Self report Language: Thai	DSM-IV MINI	a) No COI declaration b) Funding acknowledged (academic /health research institutions)
Persoons et al. (2003)	Country: Belgium Setting: Hospital (otolaryngology patients) Age (yrs): M = 48.2 (SD = 12.9)	N = 268 (97 received MINI) Depressed: 16.5%	Administration: Self-report Language: Dutch	DSM-IV MINI	a) No COI declaration b) Funding acknowledged (academic /health research institutions) and Pfizer Belgium

	Female: 65.6%				
Picardi et al. (2005)	Country: Italy Setting: Hospital (dermatology inpatients) Age (yrs): M = 37.5 Female: 56%	N = 141 Depressed: 8.5%	Administration: Self-report Language: Italian	DSM-IV SCID	a) No COI declaration b) Funding acknowledged (academic /health research institutions). Acknowledged Pfizer Italia SRL for providing the Italian version of the PHQ-9 and for permission to use it.
Stafford et al. (2007)	Country: Australia Setting: Hospital (cardiology patients) Age (yrs): M = 64.1 (SD = 10.3)	N = 193 Depressed: 18%	Administration: Self-report Language: English	DSM–IV MINI	a) No COI declaration b) Funding acknowledged (academic/health research institutions)

Thombs et al. (2008)	Female: 66% Country: US Setting: Hospital (outpatients with coronary heart disease) Age (yrs): M = 67 (SD = 11) Female: 18%	N = 1024 Depressed: 22%	Administration: Not stated Language: English	DSM C-DIS	a) COI declaration "None disclosed" b) Funding acknowledged (academic/health research institutions)
Thompson et al. (2010)	Country: US	N = 214	Administration: Self administered	DSM-IV SCID	a) No COI declaration b) Funding acknowledged (academic/health research institutions)

	Setting: Patients with Parkinson Disease Age (yrs): 72.5 (SD = 9.6) Female: 42%	Depressed: 14%	Language: English		
Turner et al. (2012)	Country: Australia Setting: Stroke patients Age (yrs): 66.7 (SD = 13.1) Female: 47.2%	N = 72	Administration: Self administered	DSM-IV SCID	a) COI declaration: Disclosures 'None'. b) Funding acknowledged (academic/health research institutions)
van Steenbergen-Weijenburg (2010)	Country: Netherlands	N = 197	Administration: Self administered	DSM-IV	a) COI declaration: 'The authors declare that they have no competing interests'. b) Funding acknowledged (academic/health research institutions) – 'this had no influence on the content of this article'.

	Setting: Diabetes patients Age (yrs): M = 61.8 (SD = 13.6) Female: 48.7% Country: Netherlands	Depressed: 18.8% N = 1338	Language: Dutch Administration: Self-report	SCID DSM-IV	a) COI declaration 'The authors declare that they have no competing interests.' b) Funding acknowledged (academic/health research institutions).
Zuitthoff et al. (2010)	Setting: Primary care Age (yrs): M = 51 (sd = 16.7) Female: 63%	Depressed: 13%	Language: Dutch	CIDI	

Table 2: Descriptive characteristics of the summed items scoring method studies cut-off point 10 (Moriarty et al, 2015)

Study	Sample characteristics	Sample size and % MDD	PHQ-9 characteristics	Diagnostic standard	a) Conflict of interest (COI) declaration b) Funding c) Relationship with original developers
13. Gräfe et al. (2004)	Country: Germany Setting: psychosomatic walk-in clinics and family practices Mean age: 41.9 (SD = 13.8) Female: 67.8%	N = 528 Depressed: 29.2% psychosomatic patients; 6.16% medical patients	Administration: self-report Language: German Cut-offs: 10 to 14	DSM-IV SCID	c) No COI declaration d) Acknowledged funding from Pfizer e) Not acknowledged
16. Kroenke et al. (2001)	Country: USA Setting: Primary care Mean age: 46 (SD=17) Female: 66%	N = 580 7.1% MDD	Administration: Self-report Language: English Cut-offs: 9 to 15	DSM-IV SCID	a) No COI declaration b) Acknowledged funding from Pfizer c) N/A
22. Navinés et al.	Country: Spain	N = 500	Administration: Self-	DSM–IV	`a) All authors declared

(2012)	Setting: General hospital (patients with chronic HCV) Mean age: 43.4 (SD = 10.2) Female: 28.6%	6.4% MDD	report Language: Spanish Cut-offs: 10	SCID	that they had no COI. b) Role of funding source declared c) Not acknowledged
29. Thekkumpurath et al. (2010)	Country: UK Setting: Hospital (cancer patients) Mean age: 61 Female: 63%	N = 782 6.3% MDD (of the whole sample)	Administration: Not stated Language: English Cut-offs: 5 to 10	DSM-IV SCID	c) COI declaration: 'Supported by Cancer Research UK' d) As in a) e) Not acknowledged
33. Williams et al. (2005)	Country: USA Setting: Secondary care (Post-stroke) Mean age: Unclear Female: Unclear	N = 316 33.5% MDD	Administration: Unclear Language: English Cut-offs: 10	DSM-IV SCID	c) No COI declaration d) Funding acknowledged (academic institutions) e) Not acknowledged

Study	Sample characteristics	Sample size and % MDD	PHQ-9 characteristics	Diagnostic standar	d) Conflict of interest declaration e) Funding

				d	
1. Adewuya et al. (2006)	Country: Nigeria Setting: community (students) Mean age: 24.8 (15-40) Female: 41.2%	N = 512 2.5% MDD	Administration: Self-report Language: English Cut-offs: 8 to 12	DSM-IV MINI	a) No COI declaration b) No funding declaration
2. Arroll et al. (2010)	Country: New Zealand Setting: Primary care Mean age: 49 (17-99) Female: 61%	N = 2642 6.2% MDD	Administration: Not stated Language: English Cut-offs: 8,10,12,15	DSM-IV SCID	a) No COI declaration b) Funding acknowledged (academic /health research institutions)
3. Azah et al. (2005)	Country: Malaysia Setting: Primary care Mean age: 38.7 (18-79) Female: 61.7%	N = 180 16.6% MDD	Administration: Self-report Language: Malay Cut-offs: 5 to 12	DSM-IV CIDI	b) No COI declaration c) Funding acknowledged (academic /health research institutions)
4. Chagas et al. (2013)	Country: Brazil	N = 84	Administration: self-report	DSM-IV SCID	a) COI declaration "None declared"

	Setting: Secondary care Mean age: Not stated Female: 52.7%	25.5% MDD	Language: Brazilian Cut-offs: 7 to 10		b) Funding acknowledged (academic/health research institutions)
6. de Lima Osorio et al. (2009)	Country: Brazil Setting: Primary care Mean age: Unclear Female: 100%	N = 177 34% MDD	Administration: research assistants Language: Brazilian Portuguese Cut-offs: 10 to 15	DSM-IV SCID	a) No COI declaration b) Funding acknowledged (academic institutions)
7. Elderon et al. (2011)	Country: USA Setting: Secondary care Mean age: Unclear Female: 18%	N = 1022 18.3% MDD	Administration: self-report Language: English Cut-offs: 10	C-DIS	a) COI declaration – 'No disclosures' b) Funding acknowledged (academic institutions and industry – AHA Pharmaceuticals Roundtable) – 'The funding organisations had no role in the design or conduct of the study, collection, management, analysis or interpretation of

					data; or preparation, review or approval of the manuscript.'
8. Fann et al. (2005)	Country: US Setting: Trauma hospital (inpatients with traumatic brain injury) Mean age: 42 (SD=17.9) Female: 29.1%	N = 135 16.3% MDD	Administration: Telephone-administered Language: English Cut-offs: 10	DSM-IV SCID	b) No COI declaration c) Funding acknowledged (academic institutions)
9. Fine et al. (2013)	Country: USA Setting: Primary care (Ohio Army National Guard) Mean age: 31 (17-60) Female: 12%	N = 498 21.5% MDD	Administration: Telephone-administered Language: English Cut-offs: 10,15	DSM-IV SCID-I	a) COI – last author disclosed financial and consulting interests (Pfizer not one of them). All other authors declared that they have no COI. b) Funding acknowledged – DoD Medical Research. ''The sponsor had no role in study design, data collection, analysis,

					interpretation of results, report writing or manuscript submission.
10. Gelaye et al. (2013)	Country: Ethiopia Setting: General hospital Mean age: 34.9 (SD=11.6) Female: 63.1 %	N = 363 12.6% MDD	Administration: Researcher-administered Language: Amharic Cut-offs: 9 to 11	DSM-IV SCAN	c) No COI declaration d) Funding acknowledged (academic /health research institutions)
11. Gilbody et al. (2007)	Country: UK Setting: Primary care Mean age: 42.5 (SD 13.6) Female: 77%	N = 96 37.5 MDD	Administration: Not stated Language: English Cut-offs: 9 to 13	DSM-IV SCID	a) COI declaration – last author involved in the development of one of the instruments (CORE-OM), 'but does not gain financially from its use. b) Funding acknowledged (academic /health research institutions)
12. Gjerdingen et	Country: USA	N = 438	Administration:	DSM-IV	c) No COI declaration

al. (2009)	Setting: Community Mean age: 29.3 Female: 100%	4.6% MDD	Telephone or self-report Language: English Cut-offs: 10	SCID	d) Funding acknowledged (academic /health research institutions)
14. Hyphantis et al. (2011)	Country: Greece Setting: Hospital – rheumatology patients Mean age: 54.2 (SD = 13.5) Female: 74%	N = 213 32.4% MDD	Administration: Researcher administered Language: Greek Cut-offs: 4 to 16	DSM-IV MINI	c) No COI declaration d) No funding acknowledgement
15. Khamseh et al. (2011)	Country: Iran Setting: Outpatient diabetic clinic Mean age: 56.1 (SD=9.6) Female: 51.8%	N = 185 43.2% MDD	Administration: Self-report Language: Persian Cut-offs: 10,13	DSM-IV SCID	c) COI declaration: The authors declared no competing interests d) Funding acknowledged (academic /health research institutions)

19. Liu et al. (2011)	Country: Taiwan Setting: Primary care Mean age: Not specified Female: 60.9%	N = 1532 3.3% MDD	Administration: Self-report Language: Chinese version Cut-offs: 9 to 11	SCAN	a) a) No COI declaration b) Funding acknowledged (academic /health research institutions)
20. Lotrakul et al. (2008)	Country: Thailand Setting: Primary care Mean age: 45.0 (SD = 14.30) Female: 73.7%	N = 279 6.8% MDD	Administration: Self report Language: Thai Cut-offs: 7 to 15	DSM-IV MINI	c) No COI declaration d) Funding acknowledged (academic /health research institutions)
23. Patel et al. (2008)	Country: India Setting: Primary care Mean age: 37.5 (18-83) Female: 56.4%	N = 299 4.3% MDD	Administration: Face-to-face interview Language: Not specified Cut-offs: 7 to 15	CIS-R	a) COI declaration – No Declaration of Interest b) Funding acknowledged (academic /health research institutions)
24. Phelan et al. (2010)	Country: USA Setting: Primary care	N = 71 12% MDD	Administration: Research assistant	DSM-IV SCID	a) COI declaration – No competing interests

	(elderly) Mean age: 78 (SD=7) Female: 62%		Language: English Cut-offs: 8 to 12		b) Funding acknowledged (academic /health research institutions) . 'The funder had no role in the study design, methods, data collection, analysis or interpretation of data, nor any role in the preparation of the manuscript or decision to submit the manuscript for publication.
25. Rooney et al. (2013)	Country: UK Setting: Secondary care (glioma) Mean age: 54.2 (SD=12.3) Female: 42.6%	N = 129 13.5% MDD	Administration: Self-report Language: English Cut-offs: 8 to 11	DSM-IV SCID	a) COI declaration "The authors declare that they have no COI" b) Funding acknowledged (academic/health research institutions)
26. Sherina et al. (2012)	Country: Malaysia Setting: Primary care	N= 146 21.2% MDD	Administration: Self-report	CIDI	a) COI declaration "The authors declare that they

	Mean age: 30.9 (18-81) Female: 100%		Language: Malay Cut-offs: 10		have no competing interests" b) Funding acknowledged (academic/health research institutions)
27. Sidebottom et al. (2012)	Country: USA Setting: Community (prenatal) Mean age: 23 (SD=5.5) Female: 100%	N = 745 3.6% MDD	Administration: Interview Language: English Cut-offs: 10	DSM-IV SCID	a) COI declaration "The authors declare that they have no financial COI" b) Funding acknowledged (academic/health research institutions)
28. Stafford et al. (2007)	Country: Australia Setting: Secondary care (cardiac procedures) Mean age: 64.14 (38-91) Female: 19.2%	N = 193 18.1% MDD	Administration: Self-report Language: English Cut-offs: 10	DSM-IV MINI	b) No COI declaration c) Funding acknowledged (academic/health research institutions)
30. Thombs et al. (2008)	Country: US Setting: Hospital (outpatients with coronary heart disease) Mean age: 67 (SD = 11)	N = 1024 22% MDD	Administration: Not stated Language: English Cut-offs: 7 to 10	DSM C-DIS	b) COI declaration "None disclosed" b) Funding acknowledged (academic/health research institutions)

	Female: 18%				
32. Watnick et al. (2005)	Country: USA Setting: Secondary care (dialysis) Mean age: 63 (SD=15) Female: 32.3%	N = 62 19% MDD	Administration: Self-report Language: English Cut-offs: 10	DSM-IV SCID	a) No COI declaration b) Funding acknowledged (academic/health research institutions)
34. Wittkampf et al. (2009)	Country: Netherlands Setting: Primary care Mean age: 49.8 Female: 66.7%	N = 664 12.3% MDD	Administration: Self-report Language: Not specified Cut-offs: 10 and 15	DSM-IV SCIDI	a) No COI declaration b) Funding acknowledged (academic/health research institutions)
35. Zhang et al. (2013)	Country: Hong Kong Setting: Secondary care (diabetic outpatients) Mean age: 55.1 (SD=9.5) Female: 40.8%	N = 99 23.2% MDD	Administration: Self-report Language: Chinese version Cut-offs: 15	DSM-IV MINI	a) COI declaration – last author acknowledged financial COI. The other authors declare that they have no competing interests. b)) Funding

					acknowledged (academic/health research institutions)
36. Zuithoff et al. (2010)	Country: Netherlands Setting: Primary care Age (yrs): M = 51 (sd = 16.7) Female: 63%	N = 1338 Depressed: 13%	Administration: Self-report Language: Dutch	DSM-IV CIDI	b) COI declaration "The authors declare that they have no competing interests. b) Funding acknowledged (academic/health research institutions)

Table 3: Quality assessment of included studies in the algorithm meta-analysis (Manea et al., 2014)

Study	**Patient selection:** Consecutive or random sample	**Patient selection:** Avoid case-control / avoid artificially inflated base rate	**Patient selection:** Avoided inappropriate exclusions	**Patient selection:** Overall risk of bias	**Index test:** PHQ-9 interpreted blind to reference test	**Index test:** If translated, appropriate translation	**Index test:** If translated, psychometric properties reported	**Index test:** Overall risk of bias
Diez-Quevedo et al. (2001)	×	✓	×	High	?	✓	✓	Unclear
Gräfe et al. (2004)	✓	✓	✓	Low	?	✓	✓	Unclear
Lowe et al. (2004)	×	✓	✓	High	✓	✓	✓	Low
Muramatsu et al. (2007)	?	✓	?	Unclear	✓	✓	?	Unclear
Navines et al. (2012)	✓	✓	✓	Low	✓	✓	?	Unclear
Spitzer et al. (1999)	×	✓	✓	High	✓	n/a	n/a	Low
Thekkumpurath et al. (2010)	×	×	✓	High	✓	n/a	n/a	Low
Arroll et al. (2010)	✓	✓	✓	Low	✓	n/a	n/a	Low
Ayalon et al. (2010)	?	✓	✓	Unclear	?	✓	?	Unclear
Eack et al. (2006)	?	✓	?	Unclear	?	n/a	n/a	Unclear
Fann et al. (2005)	✓	×	×	High	✓	n/a	n/a	Low
Gelaye et al. (2013)	?	×	?	High	✓	✓	?	Unclear
Gjerdingen et al. (2009)	✓	✓	✓	Low	?	n/a	n/a	Unclear
Henkel et al. (2004)	✓	✓	✓	Low	?	n/a	n/a	Unclear
Hyphantis et al. (2011)	✓	✓	×	High	✓	?	?	Unclear

Inagaki et al. (2013)	✓	×	✓	High	✓	?	?	Unclear
Khamseh et al. (2011)	✓	✓	?	Unclear	✓	✓	?	Unclear
Lamers et al (2008)	✓	×	×	High	✓	?	?	Unclear
Lotrakul et al. (2008)	×	✓	?	High	✓	✓	?	Unclear
Persoons et al. (2003)	✓	✓	✓	Low	✓	✓	n/a	Low
Picardi et al. (2005)	✓	✓	✓	Low	✓	?	?	Unclear
Stafford et al. (2007)	✓	✓	✓	Low	✓	n/a	n/a	Low
Thombs et al. (2008)	×	✓	?	Unclear	?	n/a	n/a	Unclear
Thomspon et al. (2011)	?	✓	✓	Unclear	?	n/a	n/a	Unclear
Turner et al. (2012)	✓	✓	✓	Low	✓	n/a	n/a	Low
Van Steenbergen-Wijenburg (2010)	?	✓	✓	Unclear	?	?	?	Unclear
Zuithoff et al. (2010)	✓	✓	✓	Low	✓	✓	?	Unclear

✓ = criterion met; × = criterion not met; ? = insufficient information to code whether criterion met; n/a = not applicable

[1]If studies reported multiple cut-off points, 'threshold pre-specified' is coded as not applicable.

Table 3: Quality assessment of included studies in the algorithm meta-analysis (Manea et al., 2015) (continued)

Study	Reference test: Reference test correctly classifies target condition	Reference test: Reference test interpreted blind to PHQ-9	Reference test: If translated, appropriate translation	Reference test: If translated, psychometric properties reported	Reference test: Overall risk of bias	Flow / timing: Interval of two weeks or less	Flow / timing: All participants receive same reference test	Flow / timing: All participants included in analysis?	Flow / timing: Overall risk of bias
Diez-Quevedo et al. (2001)	✓	✓	✓	?	Unclear	✓	✓	✓	Low
Gräfe et al. (2004)	✓	?	n/a	n/a	Unclear	✓	✓	✓	Low
Lowe et al. (2004)	✓	✓	n/a	n/a	Low	✓	✓	✓	Low
Muramatsu et al. (2007)	✓	✓	✓	✓	Low	✓	✓	?	Unclear
Navines et al. (2012)	✓	✓	?	?	Unclear	✓	✓	✓	Low
Spitzer et al. (1999)	✓	✓	n/a	n/a	Low	✓	✓	×	High
Thekkumpurath et al. (2010)	✓	✓	n/a	n/a	Low	?	✓	×	High
Arroll et al. (2010)	✓	✓	n/a	n/a	Low	✓	✓	✓	Low
Ayalon et al. (2010)	✓	?	✓	?	Unclear	?	✓	✓	Unclear
Eack et al. (2006)	✓	?	n/a	n/a	Unclear	?	✓	?	Unclear
Fann et al. (2005)	✓	?	n/a	n/a	Unclear	✓	✓	×	High
Gelaye et al. (2013)	✓	✓	✓	✓	Low	✓	✓	×	High
Gjerdingen et al. (2009)	✓	?	n/a	n/a	Unclear	✓	✓	×	High
Henkel et al. (2004)	✓	?	n/a	n/a	Unclear	✓	✓	×	High

Table 4: Quality assessment of included studies in the summed item scoring method cut-off point 10 meta-analysis (Moriarty et al., 2015)

Hyphantis et al. (2011)	✓	✓	?	?	Unclear	✓	✓	×	High
Inagaki et el. (2013)	✓	✓	✓	?	Unclear	✓	✓	×	High
Khamseh et al (2011)	✓	✓	✓	?	Unclear	✓	✓	?	Unclear
Lamers et al. (2008)	✓	✓	?	?	Unclear	?	✓	×	High
Lotrakul et al. (2008)	✓	✓	✓	✓	Low	?	✓	×	High
Persoons et al. (2003)	✓	✓	?	?	Unclear	✓	✓	✓	Low
Picardi et al. (2005)	✓	✓	✓	?	Unclear	✓	✓	×	High
Stafford et al. (2007)	✓	✓	n/a	n/a	Low	✓	✓	×	High
Thombs et al. (2008)	?	✓	n/a	n/a	Unclear	✓	✓	✓	Low
Thompson et al. (2011)	✓	?	n/a	n/a	Unclear	✓	✓	×	High
Turner et al. (2012)	✓	?	n/a	n/a	Unclear	?	✓	×	High
Van Steenbergen-Wijenburg (2010)	✓	×	?	?	High	✓	✓	×	High
Zuithoff et al. (2010)	✓	✓	?	?	Unclear	?	✓	✓	Unclear

✓ = criterion met; × = criterion not met; ? = insufficient information to code whether criterion met; n/a = not applicable

Study	Patient selection: Consecutive or random sample	Patient selection: Avoid case-control / avoid artificially inflated base rate	Patient selection: Avoided inappropriate exclusions	Patient selection: Overall risk of bias	Index test: PHQ-9 interpreted blind to reference test	Index test: Was a threshold pre-sepecifed?	Index test: If translated, appropriate translation	Index test: If translated, psychometric properties reported	Index test: Overall risk of bias
13. Gräfe et al. (2004)	✓	✓	✓	Low	?	✓	✓	✓	Unclear
16. Kroenke et al. (2011)	✓	✓	✓	Low	✓	✓	n/a	n/a	Low
22. Navinés et al. (2012)	✓	✓	✓	Low	✓	✓	✓	?	Unclear
29. Thekkumpurath et al. (2010)	✗	✗	✓	High	✓	✓	n/a	n/a	Low
33. Williams et al. (2005)	✓	✓	✓	Low	?	✓	n/a	n/a	Unclear
1. Adewuya et al. (2006)	✓	✓	✗	Unclear	✓	✓	n/a	n/a	Low
2. Arroll et al. (2010)	✓	✓	✓	Low	✓	✓	n/a	n/a	Low
3. Azah et al. (2005)	✓	✗	?	High	✓	✓	✓	✓	Low
4. Chagas et al. (2013)	✓	✓	✓	Low	✓	✓	✓	✓	Low
6. de Lima Osorio et al. (2009)	✓	✗	✓	High	?	✗	n/a	n/a	High
7. Elderon et al.	✓	✓	✓	Low	✓	✓	n/a	n/a	Low

(2011)									
8. Fann et al. (2005)	✓	✗	✗	High	✓	✓	n/a	n/a	Low
9. Fine et al. (2013)	✓	✓	✓	Low	?	✓	n/a	n/a	Unclear
10. Gelaye et al. (2013)	?	✗	?	High	✓	✗	✓	?	High
11. Gilbody et al. (2007)	?	✓	?	Unclear	✓	✓	n/a	n/a	Low
12. Gjerdingen et al. (2009)	✓	✓	✓	Low	?	✓	n/a	n/a	Unclear
14. Hyphantis et al. (2011)	✓	✗	✓	High	✓	✓	?	?	Unclear
15. Khamseh et al. (2011)	✓	✓	?	Unclear	✓	✓	✓	?	Unclear
19. Liu et al. (2011)	✓	✓	?	Unclear	✓	✗	✓	?	High
20. Lotrakul et al. (2008)	✗	✓	?	Unclear	✓	✓	✓	?	Unclear
23. Patel et al. (2008)	✓	✓	✓	Low	✓	✓	?	?	Unclear
24. Phelan et al. (2010)	✗	✓	✓	High	✓	✗	n/a	n/a	High
25. Rooney et al. (2013)	✓	✓	✓	Low	?	✗	n/a	n/a	High
26. Sherina et al. (2012)	✓	✓	✗	High	✓	✓	✓	✓	Low
27. Sidebottom	✓	✓	✓	Low	✓	✓	n/a	n/a	Low

et al. (2012)									
28. Stafford et al. (2007)	✓	✓	✓	Low	✓	✓	n/a	n/a	Low
30. Thombs et al. (2008)	✗	✓	?	High	✓	?	n/a	n/a	Unclear
32. Watnick et al. (2005)	?	✗	✓	High	✓	✓	n/a	n/a	Low
34. Wittkampf et al. (2009)	✓	✓	✓	Low	✓	?	n/a	n/a	Unclear
35. Zhang et al. (2013)	✓	✓	?	Unclear	?	✓	?	?	Unclear
36. Zuithoff et al. (2010)	✓	✓	✓	Low	✓	✓	✓	?	Unclear

Table 4: Quality assessment of included studies in the summed item scoring method cut-off point 10 meta-analysis (Moriarty et al., 2015)

Study	Reference test: Reference test correctly classifies target condition	Reference test: Reference test interpreted blind to PHQ-9	Reference test: If translated, appropriate translation	Reference test: If translated, psychometric properties reported	Reference test: Overall risk of bias	Flow / timing: Interval of two weeks or less	Flow / timing: All participants receive same reference test	Flow / timing: All participants included in analysis?	Flow / timing: Overall risk of bias
13. Gräfe et al. (2004)	✓	?	n/a	n/a	Unclear	✓	✓	✓	Low
16. Kroenke et	✓	✓	n/a	n/a	Low	✓	✓	✓	Low

al. (2011)									
22. Navinés et al. (2012)	✓	✓	?	?	Unclear	✓	✓	✓	Low
29. Thekkumpurath et al. (2010)	✓	✓	n/a	n/a	Low	?	✓	✓	Unclear
33. Williams et al. (2005)	✓	?	n/a	n/a	Unclear	?	✓	✓	Unclear
1. Adewuya et al. (2006)	✓	✓	n/a	n/a	Low	✓	✓	✓	Low
2. Arroll et al. (2010)	✓	✓	n/a	n/a	Low	?	✓	✓	Unclear
3. Azah et al. (2005)	✓	✓	✓	✓	Low	✓	✓	✗	High
4. Chagas et al. (2013)	✓	✓	?	?	Unclear	✓	✓	✗	High
6. de Lima Osorio et al. (2009)	✓	?	n/a	n/a	Unclear	?	✓	✓	Unclear
7. Elderon et al. (2011)	✓	✓	n/a	n/a	Low	✓	✓	✓	Low
8. Fann et al. (2005)	✓	?	n/a	n/a	Unclear	✓	✓	✗	High
9. Fine et al. (2013)	✓	?	n/a	n/a	Unclear	?	✓	✓	Unclear
10. Gelaye et al. (2013)	✓	✓	✓	✓	Low	✓	✓	✗	High

11. Gilbody et al. (2007)	✓	✓	n/a	n/a	Low	?	✓	✓	Unclear
12. Gjerdingen et al. (2009)	✓	?	n/a	n/a	Unclear	✓	✓	✗	High
14. Hyphantis et al. (2011)	✓	✓	?	?	Unclear	✓	✓	✗	High
15. Khamseh et al. (2011)	✓	✓	✓	?	Unclear	✓	✓	?	Unclear
19. Liu et al. (2011)	✓	✓	✓	✓	Low	✓	✓	?	Unclear
20. Lotrakul et al. (2008)	✓	✓	✓	✓	Low	?	✓	✗	High
23. Patel et al. (2008)	✓	✓	✓	?	Unclear	?	✓	✗	High
24. Phelan et al. (2010)	✓	✓	n/a	n/a	Low	✓	✓	✓	Low
25. Rooney et al. (2013)	✓	?	n/a	n/a	Unclear	?	✓	✗	High
26. Sherina et al. (2012)	✓	✓	✓	✓	Low	✓	✓	✓	Low
27. Sidebottom et al. (2012)	✓	✓	n/a	n/a	Low	✓	✓	✗	High
28. Stafford et al. (2007)	✓	✓	n/a	n/a	Low	✓	✓	✗	High
30. Thombs et al. (2008)	?	✓	n/a	n/a	Unclear	✓	✓	✓	Low
32. Watnick et al. (2005)	✓	✓	n/a	n/a	Low	✓	✓	✓	Low
34. Wittkampf et al. (2009)	✓	✓	n/a	n/a	Low	?	✓	✗	High

35. Zhang et al. (2013)	✓	?	✓	✓	Unclear	✗	✓	✗	High
36. Zuithoff et al. (2010)	✓	✓	?	?	Unclear	?	✓	✓	Unclear

Table 5. Pooled estimates of diagnostic properties of the PHQ-9 at cut-off point 10 and using algorithm scoring method in the non-independent vs independent studies groups

Settings	No of studies	No of patients	Sensitivity (95% CI)	Specificity (95% CI)	Pooled positive likelihood ratio (95% CI)	Pooled negative likelihood ratio (95% CI)	Diagnostic odds ratio (95% CI)	Heterogeneity: I^2
Manea et al, 2014 SR – RA group	7	4,065	0.77 (0.70 – 0.84)	0.94 (0.90 – 0.97)	14.97 (8.39 – 26.71)	0.23 (0.17 - 0.31)	64.40 (34.15 – 121.43)	78.9%
Manea et al, 2014 SR Independent studies	21	9,900	0.48 (0.41 – 0.91)	0.94 (0.91 – 0.95)	8.26 (6.15 – 11.09)	0.54 (0.48 – 0.62)	15.05 (11.03 – 20.52)	68.1%
Moriarty et al., 2015 SR – RA group	5	6,188	0.87 (0.77 – 0.93)	0.87 (0.76 – 0.94)	7.24 (3.74 – 14.03)	0.14 (0.08 - 0.25)	49.31 (25.74 – 94.48)	55.1%
Moriarty et al., 2015 SR Independent studies	26	13,164	0.76 (0.67 – 0.83)	0.88 (0.85 – 0.91)	6.72 (5.06 – 8.92)	0.26 (0.19 - 0.37)	24.96 (14.81 – 42.08)	81.5%

Appendix 1

Figure 1: PRISMA flowchart - search and selection of included diagnostic accuracy studies for the systematic review of studies reporting diagnostic accuracy of the PHQ-9 at using the summed items scoring method (Manea et al, 2014)

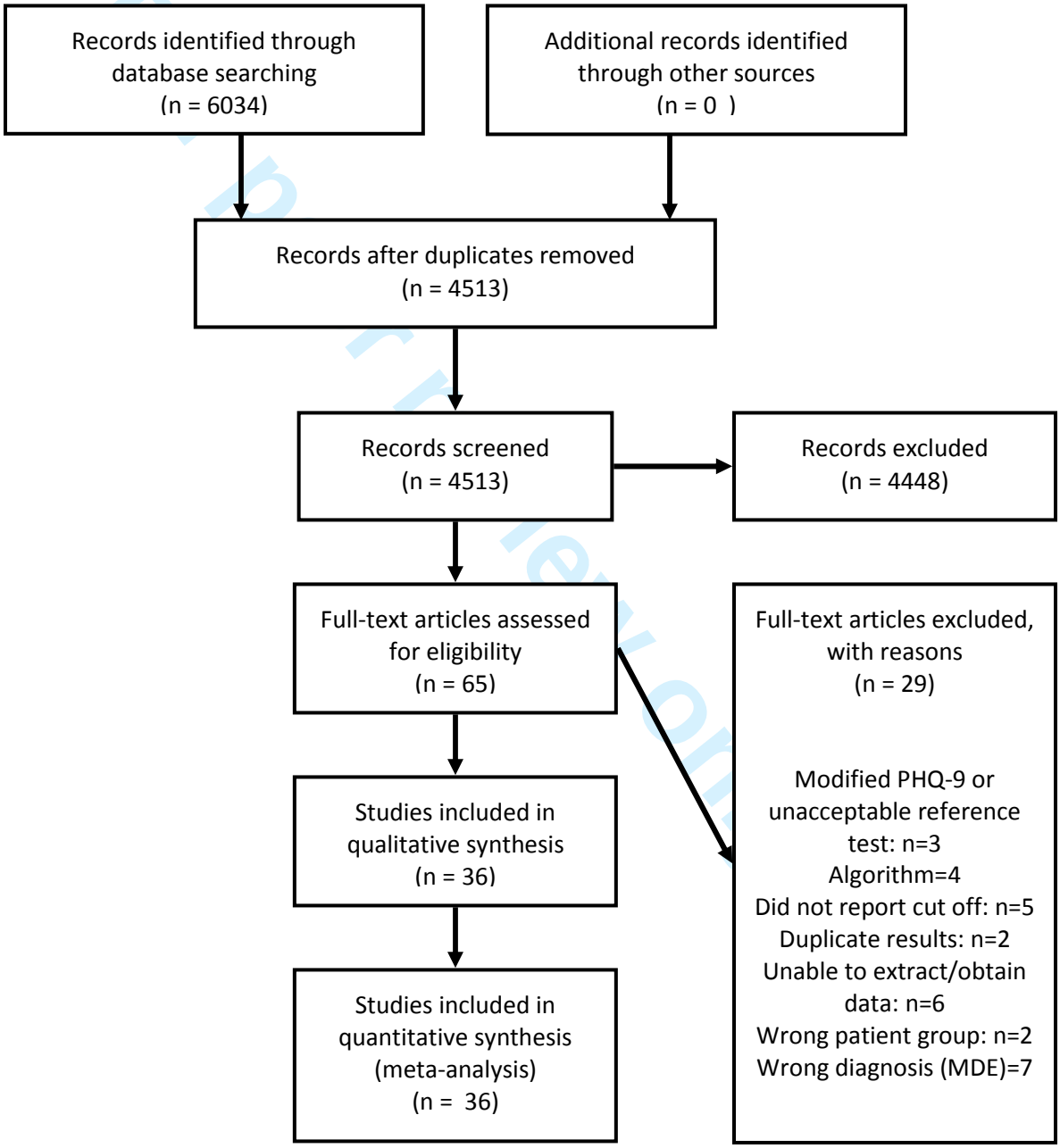
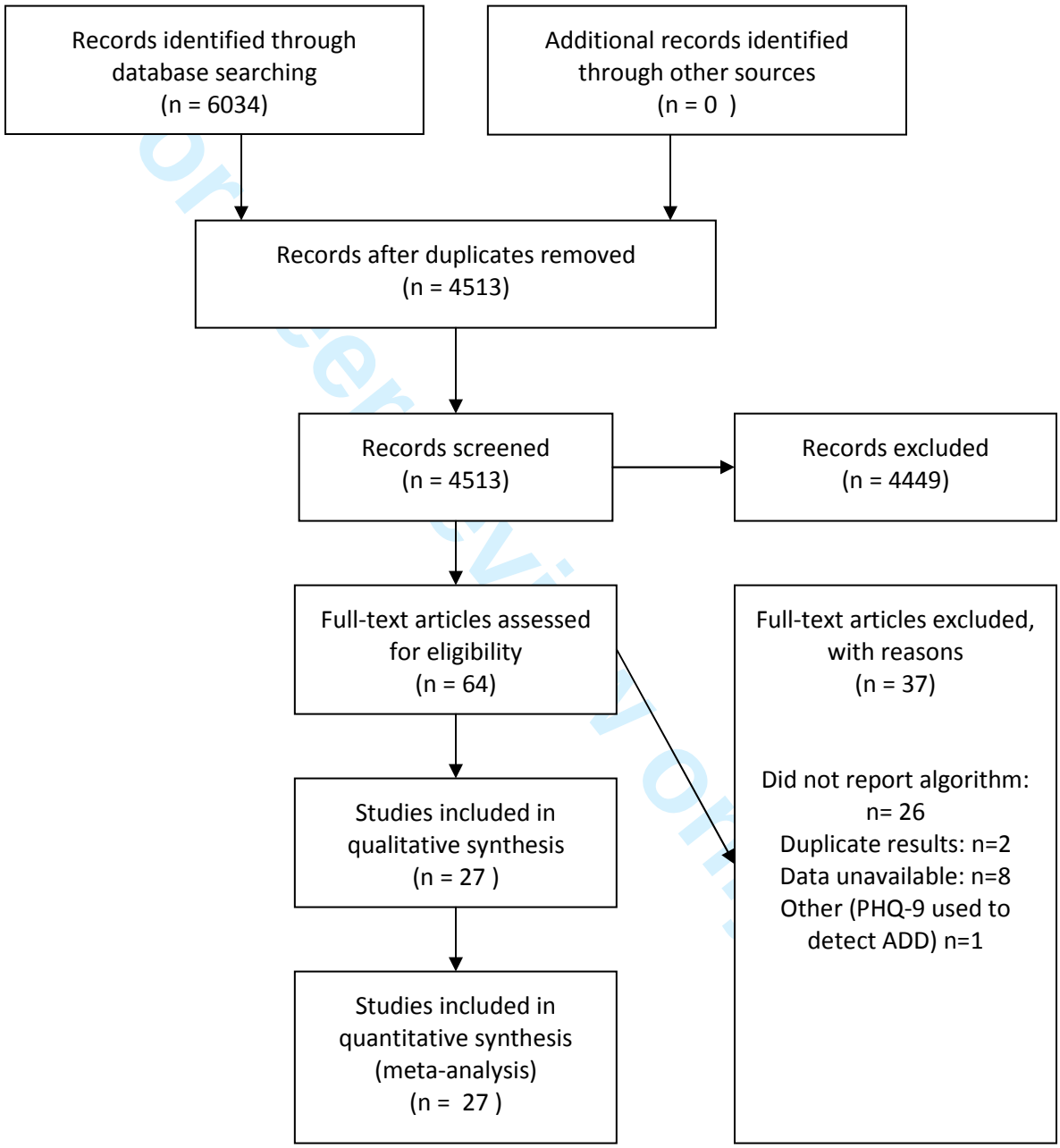


Figure 2: PRISMA flowchart - search and selection of included diagnostic accuracy studies for the systematic review of studies reporting diagnostic accuracy of the PHQ-9 at using the algorithm scoring method (Moriarty et al., 2015)



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
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).	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.	No
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
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
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Available online (see Manea et al., 2015; Moriarty et al., 2015)
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
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.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5-6
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

PRISMA 2009 Checklist

Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
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

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).	6, 21
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	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.	Tables 1 and 2
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).	Tables 3 and 4
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.	N/A
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Table 5
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Tables 3 and 4
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	11 and 17
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).	17-21
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).	21
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	21-22
FUNDING			

PRISMA 2009 Checklist

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.	23

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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Are there researcher allegiance effects in diagnostic validation studies of the PHQ-9? A systematic review and meta-analysis

Laura Manea MMedSci MRCPsych*, Jan R. Boehnke PhD, Simon Gilbody DPhil FRCPsych FRSA, Andrew S. Moriarty MRes, Dean McMillan PhD

*Corresponding Author

Hull York Medical School and Department of Health Sciences, ARRC Building, University of York, YO10 5DD

Email: laura.manea@york.ac.uk

Abstract

Objectives To investigate whether an authorship effect is found that leads to better performance in studies conducted by the original developers of the PHQ-9 (allegiant studies).

Design Systematic review with random effects bivariate diagnostic meta-analysis. Search strategies included electronic databases, examination of reference lists, and forward citation searches.

Inclusion criteria Included studies provided sufficient data to calculate the diagnostic accuracy of the PHQ-9 against a gold standard diagnosis of major depression using the algorithm or the summed item scoring method at cut-off point 10.

Data extraction Descriptive information, methodological quality criteria, and 2×2 contingency tables.

Results

Seven allegiant and twenty independent studies reported the diagnostic performance of the PHQ-9 using the algorithm scoring method. Pooled diagnostic odds ratio (DOR) for the allegiant group was 64.40, and 15.05 for non-allegiant studies group. The allegiance status was a significant predictor of DOR variation ($p < 0.0001$).

Five allegiant studies and twenty-six non-allegiant studies reported the performance of the PHQ-9 at recommended cut-off point of 10. Pooled DOR for the allegiant group was 49.31, and 24.96 for the non-allegiant studies. The allegiance status was a significant predictor of DOR variation ($P = 0.015$).

Some potential alternative explanations for the observed authorship effect including differences in study characteristics and quality were found, though it is not clear how some of them account for the observed differences

Conclusions

Allegiant studies reported better performance of the PHQ-9. Allegiance status was predictive of variation in the DOR. Based on the observed differences between independent and non-independent studies we were unable to conclude or exclude that allegiance effects are present in studies examining the diagnostic performance of the PHQ-9. This study highlights the need for future meta-analyses of diagnostic validation studies of psychological measures to evaluate the impact of researcher allegiance in the primary studies.

Strengths and limitations of this study

a) An original study–the first meta-analysis of diagnostic validation studies of psychological measures to evaluate the impact of researcher allegiance.
b) Using rigorous methodology–strict inclusion/exclusion and quality assessment criteria.
c) We found that the allegiance effect was a significant predictor of the variation of the diagnostic odds ratio in the meta-regression analysis.
d) Substantial variability observed in methodological quality of included studies.
e) Based on the observed methodological differences between the independent and non-independent studies we were unable to conclude or exclude that allegiance effects are present in studies examining the diagnostic performance of the PHQ-9.

Research on allegiance effects has a long tradition in psychotherapy research. In this context *allegiance* describes the phenomenon that researchers and clinicians who developed a treatment approach or are for other reasons invested in it tend to find larger effect sizes in favour of their treatment than for comparison groups. [1] This finding has been extensively replicated [2], [3] and is also robust when the quality of research is controlled for. Researcher allegiance is subject of on-going debates about the design of efficacy studies as well as implications for policy. [2], [4], [5] Researcher allegiance is also discussed widely in the literature on experimental as well as evaluation research. [6] Since the motivational underpinnings of allegiance effects are potentially far more ingrained into human behaviour and decision making than previously thought (e.g., [7], they may occur commonly in clinical research in general.

Although it has been suggested that allegiance effects may play a role in the validation of psychological screening and case-finding tools (e.g., O'Shea et al., in press), systematic evaluations of this hypothesis are rare and studies that acknowledge potential allegiance effects in such studies mainly come from forensic psychology and psychiatry backgrounds. [8]–[11] Diagnostic validation studies are geared at establishing the sensitivity and specificity of a screening or case finding tool, which is used in practice to differentiate cases from non-cases or to decide about whether further assessment or treatment is indicated or will be offered. An allegiance effect in such studies would be seen in systematically higher sensitivities or specificities if the original author(s) is (are) part of the team of such a study. Such a bias would have a deleterious affect on practice through promising over-optimistic accuracy of the screening or case finding tool or in evaluating the cost-effectiveness of the measure in a screening or case-finding context.

The depression module of the Patient Health Questionnaire (PHQ-9) is a widely used depression-screening instrument in non-psychiatric settings. The PHQ-9 was developed by a team of researchers, with its development underwritten by an educational grant from Pfizer US Pharmaceuticals. [12] The PHQ-9 can be scored using different methods, including an algorithm based on DSM-IV criteria and a cut-off based on summed-item scores. The psychometric properties of these two approaches have been summarised in two recently published meta-analyses. [13], [14] The goal of the current review is to investigate, based on an established database of PHQ-9 diagnostic validation studies [13], [14],

whether an allegiance effect is found that leads to an increased sensitivity and specificity in studies that were conducted by researchers closely connected to the original developers of the instrument.

METHODS

Study Selection

Similar search strategies were used in both systematic reviews. (For full details please see Manea et al. (2014) and Moriarty et al. (2015)). Embase, MEDLine and PSYCHInfo were searched from 1999 (when the PHQ-9 was first developed) to August 2013 [13] and September 2013 [14] respectively, using the terms "PHQ-9", "PHQ", "PHQ$" and "patient health questionnaire". The search strategy is presented in Appendix 2. The reference lists of studies fitting the inclusion criteria were manually searched and a reverse citation search in Web of Science was performed. Authors of unpublished studies were contacted and conference abstracts were reviewed in an attempt to minimise publication bias.

The following inclusion-exclusion criteria were used:

Population: Adult population. *Instrument:* Studies that used the PHQ-9. *Comparison (reference standard):* The accuracy of the PHQ-9 had to be assessed against a recognised gold-standard instrument for the diagnosis of either Diagnostic and Statistical Manual (DSM) or International Classification of Disease (ICD) criteria for major depression. Studies were included if the diagnoses were made using a standardised diagnostic structured interview schedule (e.g. Mini International Neuropsychiatric Interview (MINI), Structured Clinical Interview for DSM Disorders (SCID)). Unguided clinician diagnoses with no reference to a standard structured diagnostic schedule or comparisons of the PHQ-9 with other self-report measures were excluded. Studies were also excluded if the target diagnosis was not major depressive disorder (MDD, e.g. any depressive disorder). *Outcome:* Studies had to report sufficient information to calculate a 2*2 contingency table for the algorithm or the recommended cut-off point 10. *Study design:* Any design. *Additional criterion:* We avoided double counting of evidence by ensuring that only

one study of those that reported overlapping datasets in different journals were included in the meta-analysis. Citations with overlapping samples were examined to establish whether they contained information relevant to the research question that was not contained in the included report.

Quality assessment

Quality assessment was performed using the QUADAS-2 tool, a tool for evaluating the risk of bias and applicability of primary diagnostic accuracy studies when conducting diagnostic systematic reviews. [15] It covers the areas of: patient selection, index test, reference standard and flow and timing. [16] This tool was adapted for the two reviews and quality assessments were carried out by two independent reviewers for all studies included in the reviews.

Data synthesis and statistical analysis

We constructed 2x2 tables for cut-off point 10 [14] and the algorithm scoring method [13] Pooled estimates of sensitivity, specificity, positive/negative likelihood ratios, and diagnostic odds ratios were calculated using random effects bivariate meta-analysis. [17] Heterogeneity was assessed using I^2 for the diagnostic odds ratio, an estimate of the proportion of study variability that is due to between-study variability rather than sampling error. We considered values of ≥50% to indicate substantial heterogeneity.[18] Summary Receiver Operator Characteristic curves (sROC) were constructed using the bivariate model to produce a 95% confidence ellipse within ROC space. [19] Each data point in the summary ROC space represents a separate study, unlike a traditional ROC plot, which explores the effect varying thresholds on sensitivity and specificity in a single study.

We undertook a meta-regression analysis of logit diagnostic odds ratio using research allegiance as covariate in the meta-regression model. [20], [21] Analyses were conducted using STATA version 12, with the metan, metandi and metareg user-written commands.

Allegiance Rating

We rated authorship on a paper if any of the developers of the PHQ-9 - Kurt Kroenke, MD, Robert L Spitzer, MD, and Janet B W Williams – as an indicator of potential allegiance. We also rated as evidence of allegiance as acknowledged collaborations with the developers of the PHQ-9, even if they were not listed as co-authors or if the authors acknowledged funding from Pfizer to conduct the study.

RESULTS

Overview of included studies

31 studies reported the diagnostic properties of the PHQ-9 at cut-off point 10 or above and were included in this analysis. [14] 27 studies were included in the algorithm review [13]. The study selection flowcharts can be found in Appendix 1 (figures 1 and 2). The characteristics of these studies are reported in tables 1 and 2 and the results of the methodological assessment are presented in tables 3 and 4.

Algorithm scoring method

Descriptive characteristics

The descriptive characteristics of the included studies are presented in table 1. Seven individual studies that reported the diagnostic performance of the PHQ-9 using the algorithm scoring method were co-authored by the original developers of the PHQ-9 [22]–[26], specifically acknowledged one of the developers and support by an educational grant from Pfizer US [27], or were co-authored by the first author of a

previous study that had also been co-authored by one of the developers [28]. Twenty non-allegiant studies reported the diagnostic properties of the PHQ-9 using the algorithm scoring method.

Three (43%, 3/7) of the allegiant studies were conducted exclusively in hospital settings [22], [26], [28]. The remaining four studies (67%, 4/7) were conducted in different settings or non-exclusively hospital settings: one in primary care [25] and three in mixed settings: psycho-somatic walk in clinics and family practices [23][1], outpatient clinics and family practices [24] and primary care and hospital settings [27]. In the non-allegiant group, thirteen (65%, 13/20) studies were conducted in hospital settings [29]–[41]. Of the remaining seven studies, six were conducted in primary care settings [42]–[47] and one in a community sample [48].

In both groups (non-allegiant and allegiant studies), the majority of studies validated a translated version of the PHQ-9. Two of the studies authored by developers (28%, 2/7) [25], [26], and eight (40%, 8/20) allegiant studies [29], [30], [37]–[40], [42], [48] were conducted in English.

The mean prevalence of major depressive disorder in the group of allegiant studies was 13.4 % (range 6.1% - 29.2%); in the non-allegiant group it was 15.5% (range 3.9% - 32.4%). The mean age of patients in the PHQ-9 developers group was 45.7; all but one study had a mean age in the range of 40 to 50 years. In the non-allegiant group the mean age was 54.6 (range 29.3 – 75.0), with almost half (8) of the studies reporting a mean age of over 60. The percentage of females in the PHQ-9 developers was 56.8% (range 28.6% - 67.8%) and in the non-allegiant group was 59.1 (18% -100%).

[1] This study provided separate estimates for the two settings in which it was conducted; therefore separate psychometric estimates were generated for each sample for both algorithm scoring method and summed items scoring method at cut-off point 10 (see below).

All allegiant studies used a self-reported PHQ-9, whereas in 7 non-allegiant studies (30%, 6/20) the PHQ-9 was administered by a researcher [30]–[33], [43], [48]. Apart from Muramatsu et al. (2007) all allegiant studies used the SCID as a gold standard; the non-allegiant studies used a wider range of gold standards including SCAN, CIDI, MINI, and C-DIS, though the SCID was also frequently used by the independent studies as well (45%, 9/20 studies).

Four out of the seven allegiant studies (57%) did not include a conflict of interests statement [22], [23], [25], [27]. Also, four (57%) of the allegiant studies acknowledged funding from Pfizer [23]–[25], [27]. Only one study [27] acknowledged the collaboration with one of the developers of the PHQ-9.

Of the non-allegiant studies, twelve (60%) did not include a conflict of interests statement [29]–[32], [35]–[37], [39], [45], [46], [48], [49]. It appears that newer studies were more likely to include a conflict of interest statement, which may reflect a recent change in reporting. Funding was acknowledged by most studies (18/20) and most received funding from academic or/and health research institutions. Two studies received funding from pharmaceutical companies – Lundbeck [43] and Pfizer [35] and one study acknowledged that Pfizer Italia provided the Italian version of PHQ-9 and gave the authors permission to use it [36].

Diagnostic test accuracy

Pooled sensitivity and specificity was calculated separately for the non-allegiant and allegiant studies. Pooled sensitivity for the allegiant studies of the PHQ-9 was 0.77 (95% CI = 0.70 – 0.84), pooled specificity was 0.94 (95% CI = 0.90 – 0.97), and the pooled diagnostic odds ratio was 64.40 (95% CI = 34.15 – 121.43). Heterogeneity was high (I^2 = 78.9%). Figure 1 represents the summary ROCs for this set of studies.

Figure 1. PHQ-9 algorithm scoring method summary ROC plot for the diagnosis of major depressive disorder in allegiant studies (Panel A) and non-allegiant studies (Panel B). Pooled sensitivity and specificity estimates using a bi-variate meta-analysis (*HSROC* hierarchical receiver-operating characteristic).

Pooled sensitivity for the non-allegiant studies was lower compared to the developer authored studies group at 0.48 (95% CI = 0.41 – 0.91), pooled specificity was the same at 0.94 (95% CI = 0.91 – 0.95). The pooled diagnostic odds ratio was approximately four times lower at 15.05 (95% CI = 11.03 – 20.52) (see figure 1). Heterogeneity was substantial at I^2 = 68.1 %.

The meta-regression analysis for algorithm studies with non-allegiant status as the predictor of the diagnostic odds ratio showed that non-allegiant status was a significant predictor of the diagnostic odds ratio ($p < 0.0001$) and explained a substantial amount of the observed heterogeneity (51.5%).

Quality assessment

The results of the quality assessment using QUADAS-2 are given in table 3 for the studies reporting on the diagnostic performance of the algorithm scoring method. In the patient selection domain, more non-allegiant studies (65%, 13/20) than allegiant (29%, 2/7) met the criterion for consecutive referrals. There were no marked differences on the other two criteria in this domain (avoid case-control design, avoid inappropriate exclusions). In the index test domain, the proportion of studies reporting that the PHQ-9 was conducted blind to the reference test was comparable between the two groups. There were differences in this domain for those studies using a translated version of the test. All non-English allegiant studies (5/5) used an appropriately translated version of the PHQ-9; whereas just over a half of the non-allegiant studies reported this (55%, 6/11). However, the majority of both sets of studies did not report details of psychometric properties of the translated version. For the reference test domain, nearly all studies in both groups were rated as using a reference test that would correctly classify the condition. While most allegiant studies reported that the reference test was interpreted blind to the PHQ-9 score (86%, 6/7), this was reported in only 60% (12/20) of the non-allegiant studies.

The two sets of studies that used translated versions of the reference test were broadly comparable. There was a slight indication that the allegiant studies were more likely to use an appropriately translated version of the reference test and report data on the psychometric properties of the translated version, though the numbers for the translated comparison are very low. There were, however, some more notable differences on the flow and timing domain. Most allegiant studies ensured that the time between the index and reference test was under two weeks (86%, 6/7) in comparison to 70% (14/20) of the non-allegiant studies. More allegiant studies met the criterion for 'all participants included in the analysis' (57%, 4/7) than non-allegiant studies (25%).

Summed items scoring method (cut-off point 10 or above)

Descriptive characteristics

Table 2 presents the sample characteristics of the thirty-one PHQ-9 validation studies that reported the psychometric properties of the PHQ-9 at cut-off point 10 or above. Five of these studies were co-authored by the original developers of the instrument or acknowledged collaboration [12], [23], [26], [50] or were co-authored by the first author of a previous study that had also been co-authored by one of the developers [28]. Twenty-six studies were conducted by independent researchers.

Three (60%, 3/5) allegiant studies [26], [28], [50] and eleven non-allegiant studies (42%, 11/26) [30]–[32], [34], [37], [38], [51]–[55] were conducted in hospital settings.

Three (60%, 3/5) allegiant studies[12], [26], [50] and thirteen non-allegiant studies (13/26) [30], [37], [38], [42], [48], [52]–[54], [56]–[60], were conducted in English.

The mean prevalence of major depressive disorder in the allegiant group was 13.2% (range 6.1% - 33.5%) and in the non-allegiant group was 16.1% (range 2.5% - 43.2%). The mean age of patients in the allegiant group studies was 48.1 (range 41.9 -61.0) and in the 26 non-allegiant studies that reported these data was 49.1 (range 23.0 – 78.0). The percentage of females in the allegiant studies that reported these data [12], [23], [26], [28] was 56.3% (range 28.6% – 67.8%) and in the non-allegiant group was 64.9 % (range 12% -100%).

Three allegiant studies used the self-reported mode of administration and two of them did not specify how the PHQ-9 was administered. In 9 non-allegiant studies (34%, 9/26) the PHQ-9 was administered by the researcher [30]–[32], [48], [57], [59]–[62]. All allegiant studies used SCID as a gold standard; the non-allegiant studies used a wider range of gold standards including SCAN, CIDI, MINI, CIS-R, C-DIS, though the SCID was used in half of the studies (50%, 13/26 studies).

Three allegiant studies (60%) did not include a conflict of interests statement [12], [23], [50]. Two of these studies [12], [23] acknowledged funding from Pfizer. None of the allegiant studies acknowledged collaboration or authorship of one of the developers of the PHQ-9.

Of the non-allegiant studies, thirteen (42%) did not include a conflict of interests statement [30]–[32], [37], [42], [46], [48], [54], [56], [61], [63]–[65]. Similar to the algorithm studies, the newer studies were more likely to include a conflict of interest statement. Funding was acknowledged by most studies (27/31) and most received funding from academic or/and health research institutions. One study [58] acknowledged that the last author involved in the development of one of the instruments (CORE-OM), 'but does not gain financially from its use'. One study [52] acknowledged funding from industry, AHA Pharmaceuticals Roundtable, but stated that 'the funding organisations had no role in the design or conduct of the study, collection, management, analysis or interpretation of data; or preparation, review or approval of the manuscript. Fine et al., 2013 disclosed that the last author had financial and consulting interests (Pfizer was not cited as one of them).

Diagnostic test accuracy

Pooled sensitivity of allegiant studies was 0.87 (95% CI = 0.77 – 0.93), pooled specificity was 0.87 (95% CI = 0.76 – 0.94), and the pooled diagnostic odds ratio was 49.31 (95% CI = 25.74 – 94.48) – see table 5. Heterogeneity was moderate (I^2 = 55.1%). Figure 2 represents the summary ROCs for this group.

Figure 2. PHQ-9 summed items scoring method at cut-off point 10 summary ROC plot for diagnosis of major depressive disorder in allegiant studies (panel A) and non-allegiant studies (panel B). Pooled sensitivity and specificity using a bi-variate meta-analysis (*HSROC* hierarchical receiver-operating characteristic).

Pooled sensitivity of non-allegiant studies was 0.76 (95% CI, 0.67 – 0.83), pooled specificity was 0.88 95% CI (0.85 – 0.91), and the pooled diagnostic odds ratio was 24.96 (95% CI 14.81 – 42.08), approximately half that of the allegiant studies (table 2). Heterogeneity was high at I^2 = 81.5 %. Figure 2 represents the summary ROCs for this group.

The meta-regression for the studies using a cut-off point of 10 or above with allegiance status of the predictor showed that allegiance status was a significant predictor of the diagnostic odds ratio (P = 0.015) and explained 19.0% of observed heterogeneity.

Quality assessment

The results of the quality assessment using the QUADAS-2 are given in table 4. For the patient selection domain, the two groups of studies were broadly comparable on two items (consecutive or random sample, avoid case-control design). However, all allegiant studies were rated as avoiding inappropriate exclusions (5/5) in contrast to 58% (15/26) of the non-allegiant studies.

On the index test domain, there were a number of differences between the two groups of studies. More of the non-allegiant studies (81%, 21/26) reported that the PHQ-9 was interpreted blind to the reference test compared to 60% (3/5) of the allegiant studies. All (5/5) allegiant studies were rated as pre-specifying the threshold on the PHQ-9 compared to 73% (19/26) of the non-allegiant studies. The two sets of studies were broadly comparable in terms of two items from the reference test domain (correctly classify target condition, reference test interpreted blind). Only one allegiant study used a translated version of the index test or reference test, so it is not possible to comment on differences between the two sets of studies in terms of these items from the index or reference test domains. For the flow and timing domain, the two groups of studies were broadly comparable for two of the criteria (interval of two weeks or less, all participants receive same reference test). However, fewer than half of the non-allegiant studies met the criterion for 'all participants included in the analysis' (42%, 11/26); whereas all allegiant studies met this criterion.

Discussion

This is to our knowledge the first systematic examination of a possible 'allegiance' or authorship effect in the validation of screening or case finding psychological instrument for a common mental health disorder. We reviewed diagnostic validation studies of the PHQ-9, a widely used depression screening-instrument. We found that allegiant studies reported higher sensitivity paired with similar specificity compared to non-allegiant studies. When entered as a covariate in meta-regression analyses, allegiance status was predictive of variation in the DOR for both the algorithm scoring method and the summed-item scoring method at a cut-off point of 10 or above.

Previous research has proposed several possible explanations for the allegiance effect [9]–[11]. One possibility is the advertent bias that may serve to inflate the performance of a test when evaluated by those who have developed it. However, before concluding that the differences are due to this, it is important to explore and rule out alternative explanations. First, it is possible that any observed differences are a result of differences in study characteristics of the two sets of studies (e.g., setting, clinical population). Secondly, differences in the methodological quality of the studies may also account for any differences. These possibilities are examined below.

Difference in study characteristics as potential alternative explanations

The two sets of studies were broadly comparable in terms of gender and the prevalence of depression, so these variables are unlikely to offer an explanation for the differences. While there were some indications from both sets of comparisons that the PHQ-9 may have been researcher-administered more often in the independent studies, it is not immediately clear how this would lead to lowered diagnostic performance.

The diagnostic meta-analyses of the PHQ-9 [13], [14] have shown that the sensitivity and DOR of the PHQ-9 tends to be lower in hospital settings for both algorithm and summed-item scoring methods. Whilst the fact that proportionally more non-allegiant algorithm studies were conducted in secondary care could explain the lower sensitivity and DOR values in the algorithm studies, in the studies that reported the cut-off point of or above this would not be the case as proportionally more allegiant studies were conducted in hospital settings.

Similarly, differences in the proportions of studies using translated versions of the PHQ-9 are also unlikely to offer an obvious explanation of the difference in diagnostic performance, because in the algorithm set of studies more of the allegiant studies used a translated version of the test, but the proportions were in the opposite direction for the studies using a cut off of 10 or above. We tested this by carrying out a sensitivity analysis restricting the sample to English studies and studies with adequate translation. The allegiance effect was still predictive of DOR variation between allegiance and non-allegiance studies variation in both algorithm ($p = 0.00$) and summed item scoring at cut-off point of 10 meta-analyses ($p = 0.02$).

A similar conclusion is also likely to apply to the age of the samples. There were more older adults studies in the non-allegiant than allegiant studies in the algorithm comparison. Depression could be more difficult to identify in older adults due to physical co-morbidities that may present with similar symptomatology to depression and could account for the lower diagnostic performance in the non-allegiant studies. However, the non-allegiant samples in the studies that reported the psychometric properties at cut-off point 10 or above had younger samples than the allegiant studies, so this would not support this interpretation.

The SCID was used as the gold standard in nearly all allegiant studies. The fact that some non-allegiant studies used other gold standards could potentially explain the poorer psychometric properties of the PHQ-9 in these studies. The SCID is often regarded as the most valid of the available semi-structured interviews used in depression diagnostic validity studies as the reference standard. If we assume that this is the case and, furthermore, that the PHQ-9 is an accurate method of screening for depression, then the PHQ-9 may be more likely to agree with the SCID

than other reference standards. However, when we carried out a sensitivity analysis restricting the sample to SCID only studies the allegiance effect was still predictive of DOR variation between allegiance and non-allegiance studies variation in both algorithm (p = 0.01) and summed item scoring at cut-off point of 10 reviews (p= 0.02).

Differences in methodological quality as potential alternative explanations

The quality of the studies was evaluated using the QUADAS-2. Although there were several potential methodological differences between the two groups of studies from the algorithm papers, not all of these offer obvious explanations of the observed differences and some are unlikely as explanations. For example, more allegiant studies ensured that the reference test was interpreted blind to the index test. This is unlikely to account for the observed differences, because a lack of blinding is typically associated with artificially increased diagnostic performance, which is in the opposite direction to the pattern of results observed here. The impact of some other differences is less clear-cut. For example, a higher number of the non-allegiant studies met the criterion for consecutive referrals. For this to provide an explanation of the of the observed differences, the non-consecutive nature of the referrals in the studies by those who had developed the PHQ-9 would need to have led to the over-inclusion of true positives or under-inclusion of false negatives given that these studies tended to report higher sensitivity relative to the non-allegiant studies (and vice versa for the independent studies). It is not immediately obvious how this would occur. The allegiant studies were more likely to have met the criterion of 'included all participants in the analysis'. It is possible that the greater loss of participants from the non-allegiant studies may have artificially reduced the observed diagnostic accuracy, though, again, it is not immediately obvious how this would have affected the true positive and false negative rates. Although there is not an obvious explanation of how these differences in methodological quality could account for the observed differences in diagnostic performance, it is important to recognise that they cannot on that basis be ruled out.

There are, however, two differences in methodological quality among the algorithm studies that are clearer potential alternative explanations. The higher rate of appropriate translations among the allegiant studies is potentially important, because lower diagnostic estimates may be expected from studies that have poorly translated versions of the index test. In the flow and timing domain, more allegiant studies ensured that there was a less than two-week interval between the index and reference test. This is consistent with lower diagnostic performance in the non-allegiant studies: as the interval increases it is likely that depression status may change and this would lead to lower levels of agreement between the index test and the reference test.

There were also differences on some quality assessment items between the two sets of studies in the summed item scoring method comparison. The threshold was reported as pre-specified in all allegiant studies in contrast to approximately three quarters of the non-allegiant studies. On the face of it, this is unlikely to explain the observed differences, because the use of a pre-specified cut-off point is likely to be associated with lower not higher diagnostic test performance. One possibility, however, is that studies that performed poorly at this cut-off point were less likely to be reported by those who had developed the measure. As discussed in more detail in the limitations section, we were unable to explore this possibility through the use of formal tests for publication bias.

All allegiant studies avoided inappropriate exclusions compared to approximately half of the non-allegiant studies. While this is a potential alternative explanation of the differences it is not immediately obvious how this would explain the differences in diagnostic performance between the two sets of studies. Fewer than half of the non-allegiant studies met the criterion for ‘all participants included in the analysis’, in contrast to all of the allegiant studies met this criterion, but again this difference should usually work against the inclusive studies, not those

excluding cases. More of the non-allegiant studies reported that the PHQ-9 was interpreted blind to the reference test. This does offer a potential explanation, because the absence of blinding may artificially inflate diagnostic accuracy.

Limitations

The results of this review need to be viewed in the light of the limitations of the primary studies that contributed to the review and the review itself. An important consideration is to establish whether any observed differences between the diagnostic performance of the non-allegiant and allegiant studies are better accounted for by study characteristic or methodological differences. Caution, however, is needed in interpreting any differences, because of the small number of allegiant studies in both the algorithm and cut-off 10 or above comparisons. The small number of allegiant studies also meant that we were also unable to explore the potential role of publication bias in the non-allegiant and allegiant studies. At least 10 studies are required to use standard methods of examining publication bias, but the number of allegiant studies in both the algorithm and cut-off 10 or above comparisons were fewer than this.

Conclusions and implications for further research.

The aims of the review was to investigate whether an allegiance effect is found that leads to an increased diagnostic performance in diagnostic validation studies that were conducted by teams connected to the original developers of the PHQ-9. Our analyses showed that diagnostic studies conducted by independent/non-allegiant researchers had lower sensitivity paired with similar specificity compared to studies that were classified as allegiant. This conclusion held for both the algorithm and cut-off 10 or above studies. We explored a range of possible alternative

explanations for the observed allegiance effect including both differences in study characteristics and study quality. A number of potential differences were found, though for some of these it is not clear how they would necessarily account for the observed differences. However, there were a number of differences that offered potential alternative explanations unconnected to allegiance effects. In the algorithm studies, the studies rated as allegiant were also more likely to use an appropriate translation of the PHQ-9 and were also more likely to ensure that the index and reference test were conducted within two weeks of each other, both of which may be associated with an improvement in observed diagnostic performance of an instrument. The majority of studies in both meta-analyses did not provide clear statements about potential conflict of interest and/or funding, however the newer studies were more likely to provide such statements, which may reflect increasing transparency in this area of research.

We cannot, therefore, conclude that allegiance effects are present in studies examining the diagnostic performance of the PHQ-9; but nor can we rule them out. Conflicts of interest are an important area of investigation in medical and behavioural research, particularly due to concerns about trial results being influenced by industry sponsorship. Future diagnostic validity in this area should as a matter of routine present clear statements about potential conflicts of interest and funding, particularly relating to the development of the instrument under evaluation. Future meta-analyses of diagnostic validation studies of psychological measures should routinely evaluate the impact of researcher allegiance in the primary studies examined in the meta-analysis.

Contributors LM led on all stages of the review and is the guarantor. We used an established database of diagnostic validation studies of the PHQ-9 [13], [14] SG provided expert advice on methodology and approaches to assessment of the evidence base. AM carried out the literature

searches, screened the studies, extracted data and assessed the quality of the included studies for one of the systematic reviews (Moriarty et al., 2015) . LM carried out the literature searches, screened the studies, extracted data and assessed the quality of the included studies for the other systematic review (Manea et al., 2015), analysed the data for both systematic reviews and drafted the report. JB was involved in the development of the study, wrote the introduction section of the review and contributed to the production of the final report. DM supervised the quality assessment, methodology and approaches to evidence synthesis, provided senior advice and support throughout and contributed to the production of the final report. All parties were involved in drafting and/or commenting on the report.

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Table 1: Descriptive characteristics of algorithm studies (Manea et al., 2014)					
Study	**Sample characteristics (Country, setting, age, sex)**	**Sample size and % depressed**	**PHQ-9 characteristics**	**Diagnostic standard**	**a) Conflict of interest (COI) declaration b) Funding c) Relationship with original developers**
Diez-Quevedo et al. (2001)	Country: Spain Setting: Medical and surgical tertiary hospitals Age (yrs): M=43 (SD=14.2) Female: 45.6%	N = 1003 Depressed: 8.2%	Administration: Self-report Language: Spanish	DSM-III-R SCID	a) No COI declaration b) Funding acknowledged (academic institutions) c) Not acknowledged
Gräfe et al. (2004)	Country: Germany Setting: psychosomatic walk-in clinics and family practices Age (yrs): M = 41.9 (SD = 13.8) Female: 67.8%	N = 528 Depressed: 29.2% psychosomatic patients; 6.16% medical patients	Language: German Administration: self-report	DSM-IV SCID	a) No COI declaration b) Acknowledged funding from Pfizer c) Not acknowledged

Lowe et al. (2004)	Country: Germany Setting: Outpatient clinics and family practices Age (yrs): M = 41.7 (SD = 13.8) Female: 67.1%	N = 501 Depressed: 13.2%	Administration: Self-report Language: German	DSM–IV SCID	a) COI declaration 'This study was supported by unrestricted restricted grants from Pfizer Germany and from the medical faculty of the University of Heidelberg Germany, and there are no COI.' b) Acknowledged funding from Pfizer and academic institution c) Not acknowledged
Muramatsu et al. (2007)	Country: Japan Setting: Primary care and general hospital Age (yrs): M = 43.3 (SD = 16.4) Female: 59.5%	N = 131 Depressed: 28.2%	Administration: Self-report Language: Japanese	DSM–IV MINI	a) No COI declaration b) Acknowledged funding from Pfizer c) Acknowledged one of the developers of the PHQ-9: 'The authors acknowledge Dr R L Spitzer'
Navinés et al. (2012)	Country: Spain Setting: General hospital (patients with chronic HCV) Age (yrs): M = 43.4 (SD = 10.2) Female: 28.6%	N = 500 Depressed: 6.4%	Administration: Self-report Language: Spanish	DSM–IV SCID	a) All authors declared that they had no COI. b) Role of funding source declared c) Not acknowledged

Spitzer et al. (1999)	Country: US Setting: Primary care Age (yrs): M = 46 (SD = 17.2) Female: 66%	N = 3000 (585 received SCID) Depressed: 10%	Administration: Self-report Language: English	DSM-III-R SCID	a) No COI declaration b) Acknowledged funding from Pfizer. 'Drs Spitzer and Williams receive honoraria and consulting money from Pfizer Inc, which has supported this work.' c) N/A
Thekkumpurath et al. (2010)	Country: UK Setting: Hospital (cancer patients) Age (yrs): M = 61 Female: 63%	N = 782 Depressed: 6.3% (of the whole sample)	Administration: Not stated Language: English	DSM-IV SCID	a) COI declaration: 'Supported by Cancer Research UK' b) As in a) c) Not acknowledged
Ayalon et al. (2010)	Country: Israel Age (yrs): M = 75 (SD = 8.1) Female: 40.5 %	N = 153 Depressed: 3.9 %	Administration: Researcher administered Language: Hebrew	DSM-IV SCID	a) COI declaration: 'The project was funded by an Investigator's Initiated Research Grant from Lundbeck International given to Dr Liat Ayalon. Lundbeck International had no other involvement in the project concept of design or in this paper. Per Bech has occasionally over the past 3 years until August 2008 received funding from and has been speaker or member of advisory boards for pharmaceutical companies with an interest in the drug treatment of affective disorders (Astra-Zeneca, Lilly, H. Lundbeck A/S, Lundbeck Foundation and Organon). ' b) Acknowledged funding from Lundbeck International

Eack et al. (2006)	Country: US Setting: Community mental health centers for children Age (yrs): M = 39.20 (SD 9.63) Female: 100%	N = 50 Depressed: 28%	Administration: Self-report Language: English	DSM-IV SCID	a) No COI declaration b) Funding acknowledged (academic /health research institutions)
Fann et al. (2005)	Country: US Setting: Trauma hospital (inpatients with traumatic brain injury) Age (yrs): M = 42 (SD=17.9) Female: 29.1%	N = 135 Depressed: 16.3%	Administration: Telephone-administered Language: English	DSM-IV SCID	a) No COI declaration b) Funding acknowledged (academic institutions)

Gelaye et al. (2011)	Country: Ethiopia Setting: General hospital Age (yrs): 34.9 (SD=11.6) Female: 63.1 %	N = 363 Depressed: 12.6%	Administration: Researcher-administered Language: Amharic	DSM-IV SCAN	a) No COI declaration b) Funding acknowledged (academic /health research institutions)
Gjerdingen et al. (2009)	Country: US Setting: Community Age (yrs): M = 29.3 Female: 100%	N = 438 Depressed: 4.6%	Administration: Telephone or self-report Language: English	DSM-IV SCID	a) No COI declaration b) Funding acknowledged (academic /health research institutions)
Henkel et al. (2004)	Country: Germany Setting: primary care Age (yrs): not reported Female: 74%	N = 448 Depressed: 10%	Administration: self-report Language: German	DSM-IV CIDI	a) No COI declaration b) Funding acknowledged (academic /health research institutions)

Hyphantis et al. (2011)	Country: Greece Setting: Hospital – rheumatology patients Age (yrs): M = 54.2 (SD = 13.5) Female: 74%	N = 213 Depressed: 32.4%	Administration: Researcher administered Language: Greek	DSM-IV MINI	a) No COI declaration b) No funding acknowledgement
Inagaki et al. (2013)	Country: Japan Setting: General hospital Age whole sample (yrs): M = 73.5 (SD = 12.3) Female: 59.3%	N = 104 out of 511 received MINI Depressed: 7.4%	Administration: Researcher administered Language: Japanese	DSM-IV MINI	a) COI declaration: 'The authors declare that they have no competing interests.' b) Funding acknowledged (academic /health research institutions)
Khamseh et al. (2011)	Country: Iran Setting: Diabetes clinic Age (yrs): M = 56.17 (SD = 9.60) Female: 51.9%	N = 185 Depressed: 43.2%	Administration: Self report Language: Persian	DSM-IV SCID	a) COI declaration: The authors declared no competing interests b) Funding acknowledged (academic /health research institutions)

Lamers et al. (2008)	Country: Netherlands Setting: Primary care (elderly) Age (yrs): M = 71.4 (SD = 6.90) Female: 48.2%	N = 713 Depressed: 10.7%	Administration: Self report Language: Dutch	DSM-IV MINI	a) No COI declaration b) Funding acknowledged (academic /health research institutions)
Lotrakul et al. (2008)	Country: Thailand Setting: Primary care Age (yrs): M = 45.0 (SD = 14.30) Female: 73.7%	N = 279 Depressed: 6.8%	Administration: Self report Language: Thai	DSM-IV MINI	a) No COI declaration b) Funding acknowledged (academic /health research institutions)
Persoons et al. (2003)	Country: Belgium Setting: Hospital (otolaryngology patients) Age (yrs): M = 48.2 (SD = 12.9) Female: 65.6%	N = 268 (97 received MINI) Depressed: 16.5%	Administration: Self-report Language: Dutch	DSM-IV MINI	a) No COI declaration b) Funding acknowledged (academic /health research institutions) and Pfizer Belgium

Picardi et al. (2005)	Country: Italy Setting: Hospital (dermatology inpatients) Age (yrs): M = 37.5 Female: 56%	N = 141 Depressed: 8.5%	Administration: Self-report Language: Italian	DSM-IV SCID	a) No COI declaration b) Funding acknowledged (academic /health research institutions). Acknowledged Pfizer Italia SRL for providing the Italian version of the PHQ-9 and for permission to use it.
Stafford et al. (2007)	Country: Australia Setting: Hospital (cardiology patients) Age (yrs): M = 64.1 (SD = 10.3) Female: 66%	N = 193 Depressed: 18%	Administration: Self-report Language: English	DSM–IV MINI	a) No COI declaration b) Funding acknowledged (academic/health research institutions)
Thombs et al. (2008)	Country: US Setting: Hospital (outpatients with coronary heart disease) Age (yrs): M = 67 (SD = 11) Female: 18%	N = 1024 Depressed: 22%	Administration: Not stated Language: English	DSM C-DIS	a) COI declaration “None disclosed” b) Funding acknowledged (academic/health research institutions)

Thompson et al. (2010)	Country: US Setting: Patients with Parkinson Disease Age (yrs): 72.5 (SD = 9.6) Female: 42%	N = 214 Depressed: 14%	Administration: Self administered Language: English	DSM-IV SCID	a) No COI declaration b) Funding acknowledged (academic/health research institutions)
Turner et al. (2012)	Country: Australia Setting: Stroke patients Age (yrs): 66.7 (SD = 13.1) Female: 47.2%	N = 72 Depressed: 18%	Administration: Self administered Language: English	DSM-IV SCID	a) COI declaration: Disclosures 'None'. b) Funding acknowledged (academic/health research institutions)

van Steenbergen-Weijenburg (2010)	Country: Netherlands Setting: Diabetes patients Age (yrs): M = 61.8 (SD = 13.6) Female: 48.7%	N = 197 Depressed: 18.8%	Administration: Self administered Language: Dutch	DSM-IV SCID	a) COI declaration: 'The authors declare that they have no competing interests'. b) Funding acknowledged (academic/health research institutions) – 'this had no influence on the content of this article'.
Zuitthoff et al. (2010)	Country: Netherlands Setting: Primary care Age (yrs): M = 51 (sd = 16.7) Female: 63%	N = 1338 Depressed: 13%	Administration: Self-report Language: Dutch	DSM-IV CIDI	a) COI declaration 'The authors declare that they have no competing interests.' b) Funding acknowledged (academic/health research institutions).

Table 2: Descriptive characteristics of the summed items scoring method studies cut-off point 10 (Moriarty et al, 2015)

Study	Sample characteristics	Sample size and % MDD	PHQ-9 characteristics	Diagnostic standard	Conflict of interest (COI) declaration Funding c) Relationship with original developers
13. Gräfe et al. (2004)	Country: Germany Setting: psychosomatic walk-in clinics and family practices Mean age: 41.9 (SD = 13.8) Female: 67.8%	N = 528 Depressed: 29.2% psychosomatic patients; 6.16% medical patients	Administration: self-report Language: German Cut-offs: 10 to 14	DSM-IV SCID	No COI declaration Acknowledged funding from Pfizer Not acknowledged
16. Kroenke et al. (2001)	Country: USA Setting: Primary care Mean age: 46 (SD=17) Female: 66%	N = 580 7.1% MDD	Administration: Self-report Language: English Cut-offs: 9 to 15	DSM-IV SCID	a) No COI declaration b) Acknowledged funding from Pfizer c) N/A
22. Navinés et al. (2012)	Country: Spain Setting: General hospital (patients with chronic HCV) Mean age: 43.4 (SD = 10.2) Female: 28.6%	N = 500 6.4% MDD	Administration: Self-report Language: Spanish Cut-offs: 10	DSM–IV SCID	`a) All authors declared that they had no COI. b) Role of funding source declared c) Not acknowledged
29. Thekkumpurath et al. (2010)	Country: UK Setting: Hospital (cancer patients) Mean age: 61 Female: 63%	N = 782 6.3% MDD (of the whole sample)	Administration: Not stated Language: English Cut-offs: 5 to 10	DSM-IV SCID	c) COI declaration: 'Supported by Cancer Research UK' d) As in a) e) Not acknowledged
33. Williams et al. (2005)	Country: USA	N = 316	Administration: Unclear	DSM-IV SCID	a) No COI declaration b) Funding

	Setting: Secondary care (Post-stroke) Mean age: Unclear Female: Unclear	33.5% MDD	Language: English Cut-offs: 10		acknowledged (academic institutions) c) Not acknowledged

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1. Adewuya et al. (2006)	Country: Nigeria Setting: community (students) Mean age: 24.8 (15-40) Female: 41.2%	N = 512 2.5% MDD	Administration: Self-report Language: English Cut-offs: 8 to 12	DSM-IV MINI	a) No COI declaration b) No funding declaration
2. Arroll et al. (2010)	Country: New Zealand Setting: Primary care Mean age: 49 (17-99) Female: 61%	N = 2642 6.2% MDD	Administration: Not stated Language: English Cut-offs: 8,10,12,15	DSM-IV SCID	a) No COI declaration b) Funding acknowledged (academic /health research institutions)
3. Azah et al. (2005)	Country: Malaysia Setting: Primary care Mean age: 38.7 (18-79) Female: 61.7%	N = 180 16.6% MDD	Administration: Self-report Language: Malay Cut-offs: 5 to 12	DSM-IV CIDI	b) No COI declaration c) Funding acknowledged (academic /health research institutions)
4. Chagas et al. (2013)	Country: Brazil	N = 84	Administration: self-report	DSM-IV SCID	a) COI declaration "None declared"

	Setting: Secondary care Mean age: Not stated Female: 52.7%	25.5% MDD	Language: Brazilian Cut-offs: 7 to 10		b) Funding acknowledged (academic/health research institutions)
6. de Lima Osorio et al. (2009)	Country: Brazil Setting: Primary care Mean age: Unclear Female: 100%	N = 177 34% MDD	Administration: research assistants Language: Brazilian Portuguese Cut-offs: 10 to 15	DSM-IV SCID	a) No COI declaration b) Funding acknowledged (academic institutions)
7. Elderon et al. (2011)	Country: USA Setting: Secondary care Mean age: Unclear Female: 18%	N = 1022 18.3% MDD	Administration: self-report Language: English Cut-offs: 10	C-DIS	a) COI declaration – 'No disclosures' b) Funding acknowledged (academic institutions and industry – AHA Pharmaceuticals Roundtable) – 'The funding organisations had no role in the design or conduct of the study, collection, management, analysis or interpretation of data; or preparation, review or approval of the manuscript.'
8. Fann et al. (2005)	Country: US Setting: Trauma hospital (inpatients with traumatic	N = 135 16.3% MDD	Administration: Telephone-administered Language: English	DSM-IV SCID	b) No COI declaration c) Funding acknowledged (academic

	brain injury) Mean age: 42 (SD=17.9) Female: 29.1%		Cut-offs: 10		institutions)
9. Fine et al. (2013)	Country: USA Setting: Primary care (Ohio Army National Guard) Mean age: 31 (17-60) Female: 12%	N = 498 21.5% MDD	Administration: Telephone-administered Language: English Cut-offs: 10,15	DSM-IV SCID-I	a) COI – last author disclosed financial and consulting interests (Pfizer not one of them). All other authors declared that they have no COI. b) Funding acknowledged – DoD Medical Research. ‘’The sponsor had no role in study design, data collection, analysis, interpretation of results, report writing or manuscript submission.
10. Gelaye et al. (2013)	Country: Ethiopia Setting: General hospital Mean age: 34.9 (SD=11.6) Female: 63.1 %	N = 363 12.6% MDD	Administration: Researcher-administered Language: Amharic Cut-offs: 9 to 11	DSM-IV SCAN	c) No COI declaration d) Funding acknowledged (academic /health research institutions)
11. Gilbody et al.	Country: UK	N = 96	Administration: Not	DSM-IV	a) COI declaration –

(2007)	Setting: Primary care Mean age: 42.5 (SD 13.6) Female: 77%	37.5 MDD	stated Language: English Cut-offs: 9 to 13	SCID	last author involved in the development of one of the instruments (CORE-OM), 'but does not gain financially from its use. b) Funding acknowledged (academic /health research institutions)
12. Gjerdingen et al. (2009)	Country: USA Setting: Community Mean age: 29.3 Female: 100%	N = 438 4.6% MDD	Administration: Telephone or self-report Language: English Cut-offs: 10	DSM-IV SCID	c) No COI declaration d) Funding acknowledged (academic /health research institutions)
14. Hyphantis et al. (2011)	Country: Greece Setting: Hospital – rheumatology patients Mean age: 54.2 (SD = 13.5) Female: 74%	N = 213 32.4% MDD	Administration: Researcher administered Language: Greek Cut-offs: 4 to 16	DSM-IV MINI	c) No COI declaration d) No funding acknowledgement
15. Khamseh et al. (2011)	Country: Iran Setting: Outpatient diabetic clinic Mean age: 56.1 (SD=9.6)	N = 185 43.2% MDD	Administration: Self-report Language: Persian Cut-offs: 10,13	DSM-IV SCID	c) COI declaration: The authors declared no competing interests d) Funding acknowledged (academic /health

	Female: 51.8%				research institutions)
19. Liu et al. (2011)	Country: Taiwan Setting: Primary care Mean age: Not specified Female: 60.9%	N = 1532 3.3% MDD	Administration: Self-report Language: Chinese version Cut-offs: 9 to 11	SCAN	a) a) No COI declaration b) Funding acknowledged (academic /health research institutions)
20. Lotrakul et al. (2008)	Country: Thailand Setting: Primary care Mean age: 45.0 (SD = 14.30) Female: 73.7%	N = 279 6.8% MDD	Administration: Self report Language: Thai Cut-offs: 7 to 15	DSM-IV MINI	c) No COI declaration d) Funding acknowledged (academic /health research institutions)
23. Patel et al. (2008)	Country: India Setting: Primary care Mean age: 37.5 (18-83) Female: 56.4%	N = 299 4.3% MDD	Administration: Face-to-face interview Language: Not specified Cut-offs: 7 to 15	CIS-R	a) COI declaration – No Declaration of Interest b) Funding acknowledged (academic /health research institutions)
24. Phelan et al. (2010)	Country: USA Setting: Primary care (elderly) Mean age: 78 (SD=7) Female: 62%	N = 71 12% MDD	Administration: Research assistant Language: English Cut-offs: 8 to 12	DSM-IV SCID	a) COI declaration – No competing interests b) Funding acknowledged (academic /health research institutions) . 'The funder had no role in the study design, methods,

					data collection, analysis or interpretation of data, nor any role in the preparation of the manuscript or decision to submit the manuscript for publication.
25. Rooney et al. (2013)	Country: UK Setting: Secondary care (glioma) Mean age: 54.2 (SD=12.3) Female: 42.6%	N = 129 13.5% MDD	Administration: Self-report Language: English Cut-offs: 8 to 11	DSM-IV SCID	a) COI declaration "The authors declare that they have no COI" b) Funding acknowledged (academic/health research institutions)
26. Sherina et al. (2012)	Country: Malaysia Setting: Primary care Mean age: 30.9 (18-81) Female: 100%	N= 146 21.2% MDD	Administration: Self-report Language: Malay Cut-offs: 10	CIDI	a) COI declaration "The authors declare that they have no competing interests" b) Funding acknowledged (academic/health research institutions)
27. Sidebottom et al. (2012)	Country: USA Setting: Community (prenatal) Mean age: 23 (SD=5.5) Female: 100%	N = 745 3.6% MDD	Administration: Interview Language: English Cut-offs: 10	DSM-IV SCID	b) COI declaration "The authors declare that they have no financial COI" b) Funding acknowledged (academic/health research institutions)
28. Stafford et al. (2007)	Country: Australia Setting: Secondary care (cardiac procedures)	N = 193 18.1% MDD	Administration: Self-report Language: English	DSM-IV MINI	b) No COI declaration c) Funding acknowledged (academic/health

	Mean age: 64.14 (38-91) Female: 19.2%		Cut-offs: 10		research institutions)
30. Thombs et al. (2008)	Country: US Setting: Hospital (outpatients with coronary heart disease) Mean age: 67 (SD = 11) Female: 18%	N = 1024 22% MDD	Administration: Not stated Language: English Cut-offs: 7 to 10	DSM C-DIS	b) COI declaration "None disclosed" b) Funding acknowledged (academic/health research institutions)
32. Watnick et al. (2005)	Country: USA Setting: Secondary care (dialysis) Mean age: 63 (SD=15) Female: 32.3%	N = 62 19% MDD	Administration: Self-report Language: English Cut-offs: 10	DSM-IV SCID	b) No COI declaration c) Funding acknowledged (academic/health research institutions)
34. Wittkampf et al. (2009)	Country: Netherlands Setting: Primary care Mean age: 49.8 Female: 66.7%	N = 664 12.3% MDD	Administration: Self-report Language: Not specified Cut-offs: 10 and 15	DSM-IV SCIDI	No COI declaration b) Funding acknowledged (academic/health research institutions)
35. Zhang et al. (2013)	Country: Hong Kong Setting: Secondary care (diabetic outpatients) Mean age: 55.1 (SD=9.5)	N = 99 23.2% MDD	Administration: Self-report Language: Chinese version Cut-offs: 15	DSM-IV MINI	COI declaration – last author acknowledged financial COI. The other authors declare that they have no competing interests.) Funding acknowledged

	Female: 40.8%				(academic/health research institutions)
36. Zuithoff et al. (2010)	Country: Netherlands Setting: Primary care Age (yrs): M = 51 (sd = 16.7) Female: 63%	N = 1338 Depressed: 13%	Administration: Self-report Language: Dutch	DSM-IV CIDI	b) COI declaration "The authors declare that they have no competing interests. b) Funding acknowledged (academic/health research institutions)

Table 3: Quality assessment of included studies in the algorithm meta-analysis (Manea et al., 2014)

Study	Patient selection: Consecutive or random sample	Patient selection: Avoid case-control / avoid artificially inflated base rate	Patient selection: Avoided inappropriate exclusions	Patient selection: Overall risk of bias	Index test: PHQ-9 interpreted blind to reference test	Index test: If translated, appropriate translation	Index test: If translated, psychometric properties reported	Index test: Overall risk of bias
Allegiant studies								
Diez-Quevedo et al. (2001)	×	✓	×	High	?	✓	✓	Unclear
Gräfe et al. (2004)	✓	✓	✓	Low	?	✓	✓	Unclear

Lowe et al. (2004)	×	✓	✓	High	✓	✓	✓	Low
Muramatsu et al. (2007)	?	✓	?	Unclear	✓	✓	?	Unclear
Navines et al. (2012)	✓	✓	✓	Low	✓	✓	?	Unclear
Spitzer et al. (1999)	×	✓	✓	High	✓	n/a	n/a	Low
Thekkumpurath et al. (2010)	×	×	✓	High	✓	n/a	n/a	Low
Non-allegiant studies								
Arroll et al. (2010)	✓	✓	✓	Low	✓	n/a	n/a	Low
Ayalon et al. (2010)	?	✓	✓	Unclear	?	✓	?	Unclear
Eack et al. (2006)	?	✓	?	Unclear	?	n/a	n/a	Unclear
Fann et al. (2005)	✓	×	×	High	✓	n/a	n/a	Low
Gelaye et al. (2013)	?	×	?	High	✓	✓	?	Unclear
Gjerdingen et	✓	✓	✓	Low	?	n/a	n/a	Unclear

al. (2009)								
Henkel et al. (2004)	✓	✓	✓	Low	?	n/a	n/a	Unclear
Hyphantis et al. (2011)	✓	✓	×	High	✓	?	?	Unclear
Inagaki et al. (2013)	✓	×	✓	High	✓	?	?	Unclear
Khamseh et al. (2011)	✓	✓	?	Unclear	✓	✓	?	Unclear
Lamers et al (2008)	✓	×	×	High	✓	?	?	Unclear
Lotrakul et al. (2008)	×	✓	?	High	✓	✓	?	Unclear
Persoons et al. (2003)	✓	✓	✓	Low	✓	✓	n/a	Low
Picardi et al. (2005)	✓	✓	✓	Low	✓	?	?	Unclear
Stafford et al. (2007)	✓	✓	✓	Low	✓	n/a	n/a	Low
Thombs et al. (2008)	×	✓	?	Unclear	?	n/a	n/a	Unclear
Thomspon et	?	✓	✓	Unclear	?	n/a	n/a	Unclear

al. (2011)								
Turner et al. (2012)	✓	✓	✓	Low	✓	n/a	n/a	Low
Van Steenbergen-Wijenburg (2010)	?	✓	✓	Unclear	?	?	?	Unclear
Zuithoff et al. (2010)	✓	✓	✓	Low	✓	✓	?	Unclear

✓ = criterion met; × = criterion not met; ? = insufficient information to code whether criterion met; n/a = not applicable

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Table 3: Quality assessment of included studies in the algorithm meta-analysis (Manea et al., 2014) (continued)

Study	Reference test: Reference test correctly classifies target condition	Reference test: Reference test interpreted blind to PHQ-9	Reference test: If translated, appropriate translation	Reference test: If translated, psychometric properties reported	Reference test: Overall risk of bias	Flow / timing: Interval of two weeks or less	Flow / timing: All participants receive same reference test	Flow / timing: All participants included in analysis?	Flow / timing: Overall risk of bias
Allegiant studies									
Diez-Quevedo et al. (2001)	✓	✓	✓	?	Unclear	✓	✓	✓	Low

Gräfe et al. (2004)	✓	?	n/a	n/a	Unclear	✓	✓	✓	Low
Lowe et al. (2004)	✓	✓	n/a	n/a	Low	✓	✓	✓	Low
Muramatsu et al. (2007)	✓	✓	✓	✓	Low	✓	✓	?	Unclear
Navines et al. (2012)	✓	✓	?	?	Unclear	✓	✓	✓	Low
Spitzer et al. (1999)	✓	✓	n/a	n/a	Low	✓	✓	×	High
Thekkumpurath et al. (2010)	✓	✓	n/a	n/a	Low	?	✓	×	High
Non-allegiant studies									
Arroll et al. (2010)	✓	✓	n/a	n/a	Low	✓	✓	✓	Low
Ayalon et al. (2010)	✓	?	✓	?	Unclear	?	✓	✓	Unclear
Eack et al. (2006)	✓	?	n/a	n/a	Unclear	?	✓	?	Unclear
Fann et al. (2005)	✓	?	n/a	n/a	Unclear	✓	✓	×	High
Gelaye et al.	✓	✓	✓	✓	Low	✓	✓	×	High

(2013)									
Gjerdingen et al. (2009)	✓	?	n/a	n/a	Unclear	✓	✓	×	High
Henkel et al. (2004)	✓	?	n/a	n/a	Unclear	✓	✓	×	High
Hyphantis et al. (2011)	✓	✓	?	?	Unclear	✓	✓	×	High
Inagaki et el. (2013)	✓	✓	✓	?	Unclear	✓	✓	×	High
Khamseh et al (2011)	✓	✓	✓	?	Unclear	✓	✓	?	Unclear
Lamers et al. (2008)	✓	✓	?	?	Unclear	?	✓	×	High
Lotrakul et al. (2008)	✓	✓	✓	✓	Low	?	✓	×	High
Persoons et al. (2003)	✓	✓	?	?	Unclear	✓	✓	✓	Low
Picardi et al. (2005)	✓	✓	✓	?	Unclear	✓	✓	×	High
Stafford et al. (2007)	✓	✓	n/a	n/a	Low	✓	✓	×	High
Thombs et al.	?	✓	n/a	n/a	Unclear	✓	✓	✓	Low

Table 4: Quality assessment of included studies in the summed item scoring method cut-off point 10 meta-analysis (Moriarty et al., 2015)

(2008)									
Thompson et al. (2011)	✓	?	n/a	n/a	Unclear	✓	✓	×	High
Turner et al. (2012)	✓	?	n/a	n/a	Unclear	?	✓	×	High
Van Steenbergen-Wijenburg (2010)	✓	×	?	?	High	✓	✓	×	High
Zuithoff et al. (2010)	✓	✓	?	?	Unclear	?	✓	✓	Unclear

✓ = criterion met; × = criterion not met; ? = insufficient information to code whether criterion met;
n/a = not applicable

Study	Patient selection: Consecutive or random sample	Patient selection: Avoid case-control / avoid artificially inflated base rate	Patient selection: Avoided inappropriate exclusions	Patient selection: Overall risk of bias	Index test: PHQ-9 interpreted blind to reference test	Index test: Was a threshold pre-specified?	Index test: If translated, appropriate translation	Index test: If translated, psychometric properties reported	Index test: Overall risk of bias
Allegiant studies									
13. Gräfe et al. (2004)	✓	✓	✓	Low	?	✓	✓	✓	Unclear
16. Kroenke et al. (2011)	✓	✓	✓	Low	✓	✓	n/a	n/a	Low
22. Navinés et al. (2012)	✓	✓	✓	Low	✓	✓	✓	?	Unclear
29. Thekkumpurath et al. (2010)	✗	✗	✓	High	✓	✓	n/a	n/a	Low
33. Williams et al. (2005)	✓	✓	✓	Low	?	✓	n/a	n/a	Unclear
Non-allegiant studies									
1. Adewuya et	✓	✓	✗	Unclear	✓	✓	n/a	n/a	Low

al. (2006)									
2. Arroll et al. (2010)	✓	✓	✓	Low	✓	✓	n/a	n/a	Low
3. Azah et al. (2005)	✓	✗	?	High	✓	✓	✓	✓	Low
4. Chagas et al. (2013)	✓	✓	✓	Low	✓	✓	✓	✓	Low
6. de Lima Osorio et al. (2009)	✓	✗	✓	High	?	✗	n/a	n/a	High
7. Elderon et al. (2011)	✓	✓	✓	Low	✓	✓	n/a	n/a	Low
8. Fann et al. (2005)	✓	✗	✗	High	✓	✓	n/a	n/a	Low
9. Fine et al. (2013)	✓	✓	✓	Low	?	✓	n/a	n/a	Unclear
10. Gelaye et al. (2013)	?	✗	?	High	✓	✗	✓	?	High
11. Gilbody et al.	?	✓	?	Unclear	✓	✓	n/a	n/a	Low

(2007)									
12. Gjerdingen et al. (2009)	✓	✓	✓	Low	?	✓	n/a	n/a	Unclear
14. Hyphantis et al. (2011)	✓	✗	✓	High	✓	✓	?	?	Unclear
15. Khamseh et al. (2011)	✓	✓	?	Unclear	✓	✓	✓	?	Unclear
19. Liu et al. (2011)	✓	✓	?	Unclear	✓	✗	✓	?	High
20. Lotrakul et al. (2008)	✗	✓	?	Unclear	✓	✓	✓	?	Unclear
23. Patel et al. (2008)	✓	✓	✓	Low	✓	✓	?	?	Unclear
24. Phelan et al. (2010)	✗	✓	✓	High	✓	✗	n/a	n/a	High
25. Rooney et al. (2013)	✓	✓	✓	Low	?	✗	n/a	n/a	High
26. Sherina et al.	✓	✓	✗	High	✓	✓	✓	✓	Low

(2012)									
27. Sidebottom et al. (2012)	✓	✓	✓	Low	✓	✓	n/a	n/a	Low
28. Stafford et al. (2007)	✓	✓	✓	Low	✓	✓	n/a	n/a	Low
30. Thombs et al. (2008)	✗	✓	?	High	✓	?	n/a	n/a	Unclear
32. Watnick et al. (2005)	?	✗	✓	High	✓	✓	n/a	n/a	Low
34. Wittkampf et al. (2009)	✓	✓	✓	Low	✓	?	n/a	n/a	Unclear
35. Zhang et al. (2013)	✓	✓	?	Unclear	?	✓	?	?	Unclear
36. Zuithoff et al. (2010)	✓	✓	✓	Low	✓	✓	✓	?	Unclear

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Table 4: Quality assessment of included studies in the summed item scoring method cut-off point 10 meta-analysis (Moriarty et al., 2015) (continued)

Study	Reference test: Reference test	Reference test: Reference test	Reference test: If translated,	Reference test: If translated, psychometric	Reference test: Overall risk of	Flow / timing: Interval of two	Flow / timing: All participants	Flow / timing: All participants	Flow / timing: Overall risk of

	correctly classifies target condition	interpreted blind to PHQ-9	appropriate translation	properties reported	bias	weeks or less	receive same reference test	included in analysis?	bias
Allegiant studies									
13. Gräfe et al. (2004)	✓	?	n/a	n/a	Unclear	✓	✓	✓	Low
16. Kroenke et al. (2011)	✓	✓	n/a	n/a	Low	✓	✓	✓	Low
22. Navinés et al. (2012)	✓	✓	?	?	Unclear	✓	✓	✓	Low
29. Thekkumpurath et al. (2010)	✓	✓	n/a	n/a	Low	?	✓	✓	Unclear
33. Williams et al. (2005)	✓	?	n/a	n/a	Unclear	?	✓	✓	Unclear
Non-allegiant studies									
1. Adewuya et al. (2006)	✓	✓	n/a	n/a	Low	✓	✓	✓	Low
2. Arroll et al.	✓	✓	n/a	n/a	Low	?	✓	✓	Unclear

(2010)									
3. Azah et al. (2005)	✓	✓	✓	✓	Low	✓	✓	✗	High
4. Chagas et al. (2013)	✓	✓	?	?	Unclear	✓	✓	✗	High
6. de Lima Osorio et al. (2009)	✓	?	n/a	n/a	Unclear	?	✓	✓	Unclear
7. Elderon et al. (2011)	✓	✓	n/a	n/a	Low	✓	✓	✓	Low
8. Fann et al. (2005)	✓	?	n/a	n/a	Unclear	✓	✓	✗	High
9. Fine et al. (2013)	✓	?	n/a	n/a	Unclear	?	✓	✓	Unclear
10. Gelaye et al. (2013)	✓	✓	✓	✓	Low	✓	✓	✗	High
11. Gilbody et al. (2007)	✓	✓	n/a	n/a	Low	?	✓	✓	Unclear
12. Gjerdingen	✓	?	n/a	n/a	Unclear	✓	✓	✗	High

et al. (2009)									
14. Hyphantis et al. (2011)	✓	✓	?	?	Unclear	✓	✓	✗	High
15. Khamseh et al. (2011)	✓	✓	✓	?	Unclear	✓	✓	?	Unclear
19. Liu et al. (2011)	✓	✓	✓	✓	Low	✓	✓	?	Unclear
20. Lotrakul et al. (2008)	✓	✓	✓	✓	Low	?	✓	✗	High
23. Patel et al. (2008)	✓	✓	✓	?	Unclear	?	✓	✗	High
24. Phelan et al. (2010)	✓	✓	n/a	n/a	Low	✓	✓	✓	Low
25. Rooney et al. (2013)	✓	?	n/a	n/a	Unclear	?	✓	✗	High
26. Sherina et al. (2012)	✓	✓	✓	✓	Low	✓	✓	✓	Low
27. Sidebottom	✓	✓	n/a	n/a	Low	✓	✓	✗	High

et al. (2012)									
28. Stafford et al. (2007)	✓	✓	n/a	n/a	Low	✓	✓	✗	High
30. Thombs et al. (2008)	?	✓	n/a	n/a	Unclear	✓	✓	✓	Low
32. Watnick et al. (2005)	✓	✓	n/a	n/a	Low	✓	✓	✓	Low
34. Wittkampf et al. (2009)	✓	✓	n/a	n/a	Low	?	✓	✗	High
35. Zhang et al. (2013)	✓	?	✓	✓	Unclear	✗	✓	✗	High
36. Zuithoff et al. (2010)	✓	✓	?	?	Unclear	?	✓	✓	Unclear

Table 5. Pooled estimates of diagnostic properties of the PHQ-9 at cut-off point 10 and using algorithm scoring method in the non-independent vs independent studies groups

Settings	No of studies	No of patients	Sensitivity (95% CI)	Specificity (95% CI)	Pooled positive likelihood ratio (95% CI)	Pooled negative likelihood ratio (95% CI)	Diagnostic odds ratio (95% CI)	Heterogeneity: I^2

Manea et al, 2014 SR – RA group	7	4,065	0.77 (0.70 – 0.84)	0.94 (0.90 – 0.97)	14.97 (8.39 – 26.71)	0.23 (0.17 - 0.31)	64.40 (34.15 – 121.43)	78.9%
Manea et al, 2014 SR Independent studies	21	9,900	0.48 (0.41 – 0.91)	0.94 (0.91 – 0.95)	8.26 (6.15 – 11.09)	0.54 (0.48 – 0.62)	15.05 (11.03 – 20.52)	68.1%
Moriarty et al., 2015 SR – RA group	5	6,188	0.87 (0.77 – 0.93)	0.87 (0.76 – 0.94)	7.24 (3.74 – 14.03)	0.14 (0.08 - 0.25)	49.31 (25.74 – 94.48)	55.1%
Moriarty et al., 2015 SR Independent studies	26	13,164	0.76 (0.67 – 0.83)	0.88 (0.85 – 0.91)	6.72 (5.06 – 8.92)	0.26 (0.19 - 0.37)	24.96 (14.81 – 42.08)	81.5%

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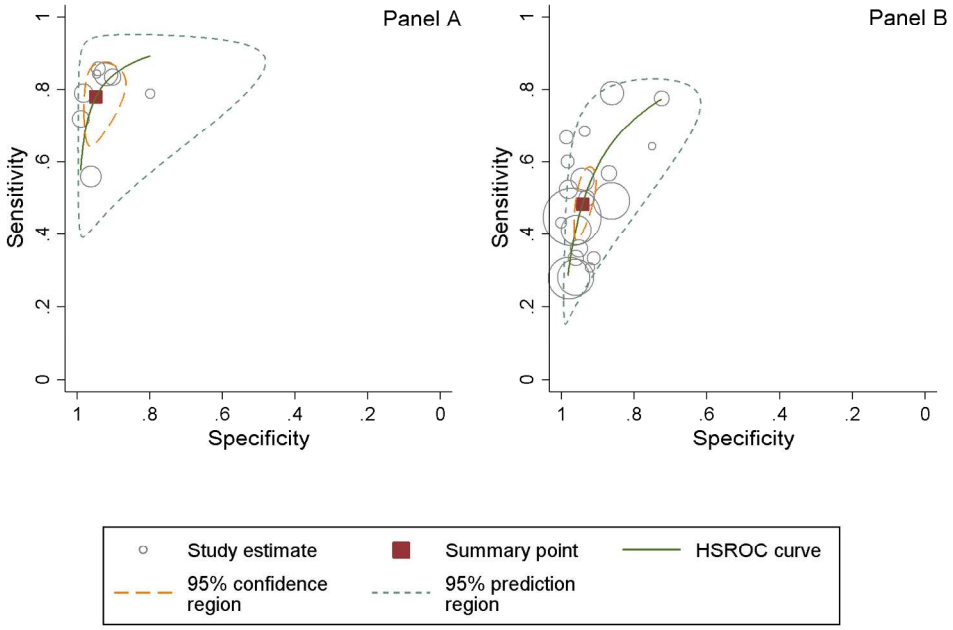
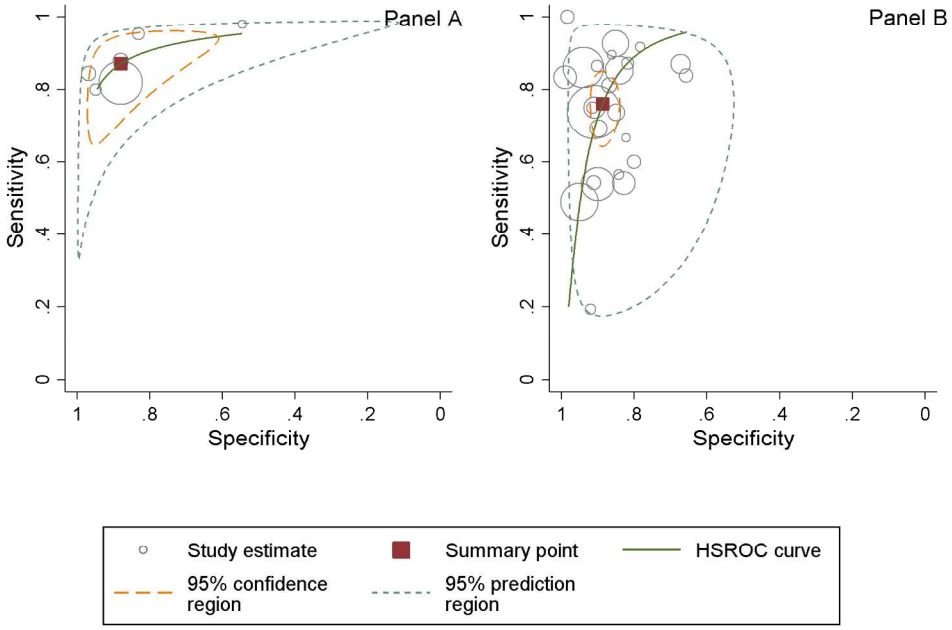


Figure 1. PHQ-9 algorithm scoring method summary ROC plot for the diagnosis of major depressive disorder in allegiant studies (Panel A) and non-allegiant studies (Panel B). Pooled sensitivity and specificity estimates using a bi-variate meta-analysis (HSROC hierarchical receiver-operating characteristic).

169x123mm (300 x 300 DPI)



Caption : Figure 2. PHQ-9 summed items scoring method at cut-off point 10 summary ROC plot for diagnosis of major depressive disorder in allegiant studies (panel A) and non-allegiant studies (panel B). Pooled sensitivity and specificity using a bi-variate meta-analysis (HSROC hierarchical receiver-operating characteristic).

169x123mm (300 x 300 DPI)

Appendices to: Manea L, Boehnke JR, Gilbody S, Moriarty AS, McMillan D, Are there researcher allegiance effects in diagnostic validation studies of the PHQ-9? A systematic review and meta-analysis. Manuscript submitted for publication at BMJOpen.

Appendix 1

Figure 1: PRISMA flowchart - search and selection of included diagnostic accuracy studies for the systematic review of studies reporting diagnostic accuracy of the PHQ-9 at using the summed items scoring method (Manea et al, 2014)

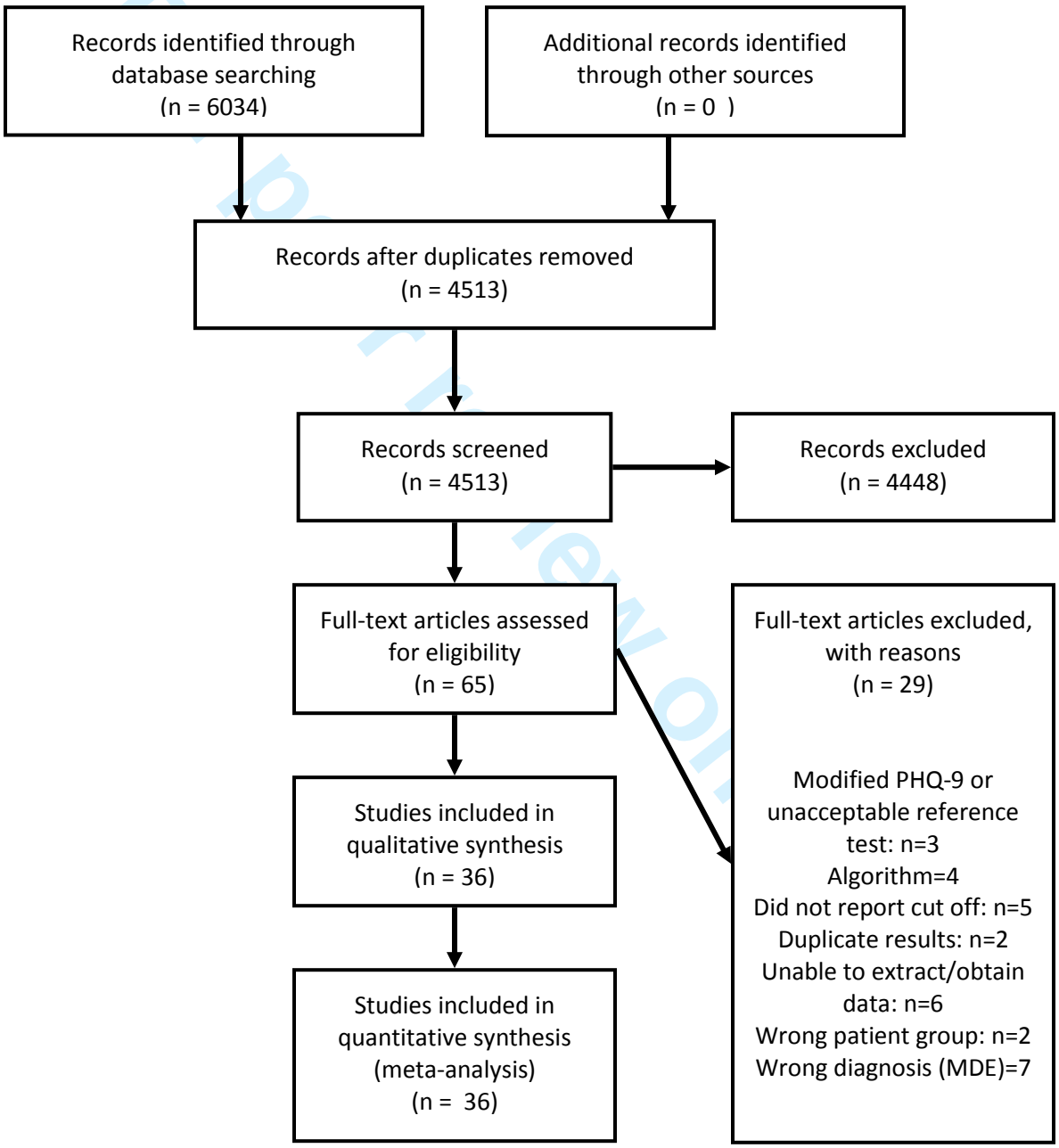
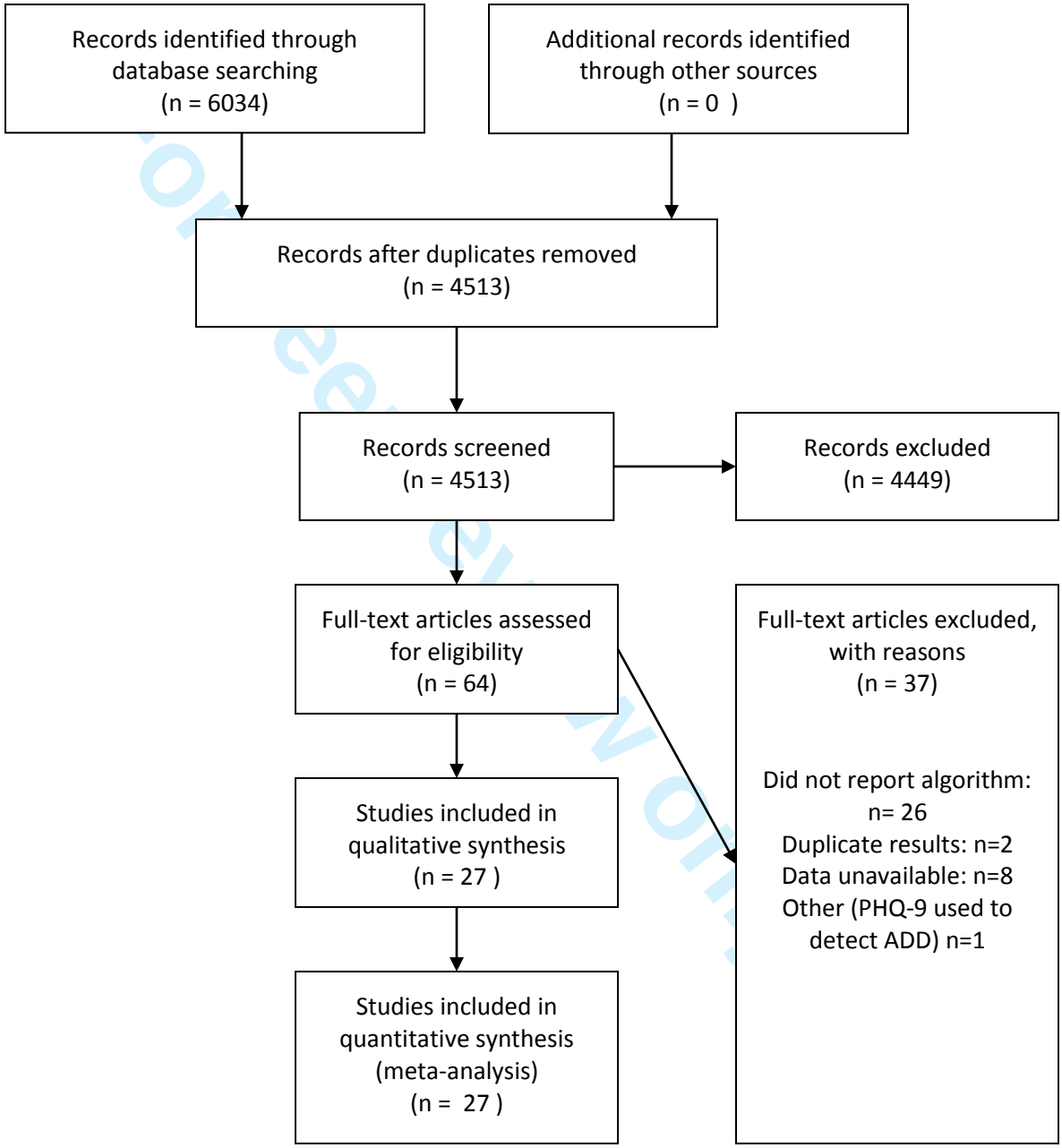


Figure 2: PRISMA flowchart - search and selection of included diagnostic accuracy studies for the systematic review of studies reporting diagnostic accuracy of the PHQ-9 at using the algorithm scoring method (Moriarty et al., 2015)



Appendix 2: Search terms used in Embase, MEDLINE and PsycINFO

(phq adj5 “9”).ti,ab.
(phq adj5 item$).ti,ab.
(patient health questionnaire adj5 “9”).ti,ab.
(patient health questionnaire adj5 item$).ti,ab.
(prime md adj5 “9”).ti,ab.
(prime md adj5 item$).ti,ab.

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
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).	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.	No
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
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
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Available online (see Manea et al., 2015; Moriarty et al., 2015)
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
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.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5-6
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

PRISMA 2009 Checklist

Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
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

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).	6, 21
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	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.	Tables 1 and 2
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).	Tables 3 and 4
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.	N/A
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Table 5
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Tables 3 and 4
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	11 and 17
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).	17-21
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).	21
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	21-22
FUNDING			

PRISMA 2009 Checklist

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.	23

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Are there researcher allegiance effects in diagnostic validation studies of the PHQ-9? A systematic review and meta-analysis

Laura Manea MMedSci MRCPsych*, Jan R. Boehnke PhD, Simon Gilbody DPhil FRCPsych FRSA, Andrew S. Moriarty MRes, Dean McMillan PhD

*Corresponding Author

Hull York Medical School and Department of Health Sciences, ARRC Building, University of York, YO10 5DD

Email: laura.manea@york.ac.uk

Abstract

Objectives To investigate whether an authorship effect is found that leads to better performance in studies conducted by the original developers of the PHQ-9 (allegiant studies).

Design Systematic review with random effects bivariate diagnostic meta-analysis. Search strategies included electronic databases, examination of reference lists, and forward citation searches.

Inclusion criteria Included studies provided sufficient data to calculate the diagnostic accuracy of the PHQ-9 against a gold standard diagnosis of major depression using the algorithm or the summed item scoring method at cut-off point 10.

Data extraction Descriptive information, methodological quality criteria, and 2×2 contingency tables.

Results

Seven allegiant and twenty independent studies reported the diagnostic performance of the PHQ-9 using the algorithm scoring method. Pooled diagnostic odds ratio (DOR) for the allegiant group was 64.40, and 15.05 for non-allegiant studies group. The allegiance status was a significant predictor of DOR variation ($p < 0.0001$).

Five allegiant studies and twenty-six non-allegiant studies reported the performance of the PHQ-9 at recommended cut-off point of 10. Pooled DOR for the allegiant group was 49.31, and 24.96 for the non-allegiant studies. The allegiance status was a significant predictor of DOR variation ($P = 0.015$).

Some potential alternative explanations for the observed authorship effect including differences in study characteristics and quality were found, though it is not clear how some of them account for the observed differences

Conclusions

Allegiant studies reported better performance of the PHQ-9. Allegiance status was predictive of variation in the DOR. Based on the observed differences between independent and non-independent studies we were unable to conclude or exclude that allegiance effects are present in studies examining the diagnostic performance of the PHQ-9. This study highlights the need for future meta-analyses of diagnostic validation studies of psychological measures to evaluate the impact of researcher allegiance in the primary studies.

Strengths and limitations of this study

a) An original study–the first meta-analysis of diagnostic validation studies of psychological measures to evaluate the impact of researcher allegiance.
b) Using rigorous methodology–strict inclusion/exclusion and quality assessment criteria.
c) We found that the allegiance effect was a significant predictor of the variation of the diagnostic odds ratio in the meta-regression analysis.
d) Substantial variability observed in methodological quality of included studies.
e) Based on the observed methodological differences between the independent and non-independent studies we were unable to conclude or exclude that allegiance effects are present in studies examining the diagnostic performance of the PHQ-9.

Research on allegiance effects has a long tradition in psychotherapy research. In this context *allegiance* describes the phenomenon that researchers and clinicians who developed a treatment approach or are for other reasons invested in it tend to find larger effect sizes in favour of their treatment than for comparison groups. [1] This finding has been extensively replicated [2], [3] and is also robust when the quality of research is controlled for. Researcher allegiance is subject of on-going debates about the design of efficacy studies as well as implications for policy. [2], [4], [5] Researcher allegiance is also discussed widely in the literature on experimental as well as evaluation research. [6] Since the motivational underpinnings of allegiance effects are potentially far more ingrained into human behaviour and decision making than previously thought (e.g., [7], they may occur commonly in clinical research in general.

Although it has been suggested that allegiance effects may play a role in the validation of psychological screening and case-finding tools (e.g., O'Shea et al., in press), systematic evaluations of this hypothesis are rare and studies that acknowledge potential allegiance effects in such studies mainly come from forensic psychology and psychiatry backgrounds. [8]–[11] Diagnostic validation studies are geared at establishing the sensitivity and specificity of a screening or case finding tool, which is used in practice to differentiate cases from non-cases or to decide about whether further assessment or treatment is indicated or will be offered. An allegiance effect in such studies would be seen in systematically higher sensitivities or specificities if the original author(s) is (are) part of the team of such a study. Such a bias would have a deleterious affect on practice through promising over-optimistic accuracy of the screening or case finding tool or in evaluating the cost-effectiveness of the measure in a screening or case-finding context.

The depression module of the Patient Health Questionnaire (PHQ-9) is a widely used depression-screening instrument in non-psychiatric settings. The PHQ-9 was developed by a team of researchers, with its development underwritten by an educational grant from Pfizer US Pharmaceuticals. [12] The PHQ-9 can be scored using different methods, including an algorithm based on DSM-IV criteria and a cut-off based on summed-item scores. The psychometric properties of these two approaches have been summarised in two recently published meta-analyses. [13], [14] The goal of the current review is to investigate, based on an established database of PHQ-9 diagnostic validation studies [13], [14],

whether an allegiance effect is found that leads to an increased sensitivity and specificity in studies that were conducted by researchers closely connected to the original developers of the instrument.

METHODS

Study Selection

Similar search strategies were used in both systematic reviews. (For full details please see Manea et al. (2014) and Moriarty et al. (2015)). Embase, MEDLine and PSYCHInfo were searched from 1999 (when the PHQ-9 was first developed) to August 2013 [13] and September 2013 [14] respectively, using the terms "PHQ-9", "PHQ", "PHQ$" and "patient health questionnaire". The search strategy is presented in Appendix 1. The reference lists of studies fitting the inclusion criteria were manually searched and a reverse citation search in Web of Science was performed. Authors of unpublished studies were contacted and conference abstracts were reviewed in an attempt to minimise publication bias.

The following inclusion-exclusion criteria were used:

Population: Adult population. *Instrument:* Studies that used the PHQ-9. *Comparison (reference standard):* The accuracy of the PHQ-9 had to be assessed against a recognised gold-standard instrument for the diagnosis of either Diagnostic and Statistical Manual (DSM) or International Classification of Disease (ICD) criteria for major depression. Studies were included if the diagnoses were made using a standardised diagnostic structured interview schedule (e.g. Mini International Neuropsychiatric Interview (MINI), Structured Clinical Interview for DSM Disorders (SCID)). Unguided clinician diagnoses with no reference to a standard structured diagnostic schedule or comparisons of the PHQ-9 with other self-report measures were excluded. Studies were also excluded if the target diagnosis was not major depressive disorder (MDD, e.g. any depressive disorder). *Outcome:* Studies had to report sufficient information to calculate a 2*2 contingency table for the algorithm or the recommended cut-off point 10. *Study design:* Any design. *Additional criterion:* We avoided double counting of evidence by ensuring that only

one study of those that reported overlapping datasets in different journals were included in the meta-analysis. Citations with overlapping samples were examined to establish whether they contained information relevant to the research question that was not contained in the included report.

Quality assessment

Quality assessment was performed using the QUADAS-2 tool, a tool for evaluating the risk of bias and applicability of primary diagnostic accuracy studies when conducting diagnostic systematic reviews. [15] It covers the areas of: patient selection, index test, reference standard and flow and timing. [16] This tool was adapted for the two reviews and quality assessments were carried out by two independent reviewers for all studies included in the reviews.

Data synthesis and statistical analysis

We constructed 2x2 tables for cut-off point 10 [14] and the algorithm scoring method [13] Pooled estimates of sensitivity, specificity, positive/negative likelihood ratios, and diagnostic odds ratios were calculated using random effects bivariate meta-analysis. [17] Heterogeneity was assessed using I^2 for the diagnostic odds ratio, an estimate of the proportion of study variability that is due to between-study variability rather than sampling error. We considered values of ≥50% to indicate substantial heterogeneity.[18] Summary Receiver Operator Characteristic curves (sROC) were constructed using the bivariate model to produce a 95% confidence ellipse within ROC space. [19] Each data point in the summary ROC space represents a separate study, unlike a traditional ROC plot, which explores the effect varying thresholds on sensitivity and specificity in a single study.

We undertook a meta-regression analysis of logit diagnostic odds ratio using research allegiance as covariate in the meta-regression model. [20], [21] Analyses were conducted using STATA version 12, with the metan, metandi and metareg user-written commands.

Allegiance Rating

We rated authorship on a paper if any of the developers of the PHQ-9 - Kurt Kroenke, MD, Robert L Spitzer, MD, and Janet B W Williams – as an indicator of potential allegiance. We also rated as evidence of allegiance as acknowledged collaborations with the developers of the PHQ-9, even if they were not listed as co-authors or if the authors acknowledged funding from Pfizer to conduct the study.

RESULTS

Overview of included studies

31 studies reported the diagnostic properties of the PHQ-9 at cut-off point 10 or above and were included in this analysis. [14] 27 studies were included in the algorithm review [13]. The study selection flowcharts can be found in Appendix 2 (figures 1 and 2). The characteristics of these studies are reported in tables 1 and 2 and the results of the methodological assessment are presented in tables 3 and 4.

Algorithm scoring method

Descriptive characteristics

The descriptive characteristics of the included studies are presented in table 1. Seven individual studies that reported the diagnostic performance of the PHQ-9 using the algorithm scoring method were co-authored by the original developers of the PHQ-9 [22]–[26], specifically acknowledged one of the developers and support by an educational grant from Pfizer US [27], or were co-authored by the first author of a

previous study that had also been co-authored by one of the developers [28]. Twenty non-allegiant studies reported the diagnostic properties of the PHQ-9 using the algorithm scoring method.

Three (43%, 3/7) of the allegiant studies were conducted exclusively in hospital settings [22], [26], [28]. The remaining four studies (67%, 4/7) were conducted in different settings or non-exclusively hospital settings: one in primary care [25] and three in mixed settings: psycho-somatic walk in clinics and family practices [23][1], outpatient clinics and family practices [24] and primary care and hospital settings [27]. In the non-allegiant group, thirteen (65%, 13/20) studies were conducted in hospital settings [29]–[41]. Of the remaining seven studies, six were conducted in primary care settings [42]–[47] and one in a community sample [48].

In both groups (non-allegiant and allegiant studies), the majority of studies validated a translated version of the PHQ-9. Two of the studies authored by developers (28%, 2/7) [25], [26], and eight (40%, 8/20) allegiant studies [29], [30], [37]–[40], [42], [48] were conducted in English.

The mean prevalence of major depressive disorder in the group of allegiant studies was 13.4 % (range 6.1% - 29.2%); in the non-allegiant group it was 15.5% (range 3.9% - 32.4%). The mean age of patients in the PHQ-9 developers group was 45.7; all but one study had a mean age in the range of 40 to 50 years. In the non-allegiant group the mean age was 54.6 (range 29.3 – 75.0), with almost half (8) of the studies reporting a mean age of over 60. The percentage of females in the PHQ-9 developers was 56.8% (range 28.6% - 67.8%) and in the non-allegiant group was 59.1 (18% -100%).

[1] This study provided separate estimates for the two settings in which it was conducted; therefore separate psychometric estimates were generated for each sample for both algorithm scoring method and summed items scoring method at cut-off point 10 (see below).

All allegiant studies used a self-reported PHQ-9, whereas in 7 non-allegiant studies (30%, 6/20) the PHQ-9 was administered by a researcher [30]–[33], [43], [48]. Apart from Muramatsu et al. (2007) all allegiant studies used the SCID as a gold standard; the non-allegiant studies used a wider range of gold standards including SCAN, CIDI, MINI, and C-DIS, though the SCID was also frequently used by the independent studies as well (45%, 9/20 studies).

Four out of the seven allegiant studies (57%) did not include a conflict of interests statement [22], [23], [25], [27]. Also, four (57%) of the allegiant studies acknowledged funding from Pfizer [23]–[25], [27]. Only one study [27] acknowledged the collaboration with one of the developers of the PHQ-9.

Of the non-allegiant studies, twelve (60%) did not include a conflict of interests statement [29]–[32], [35]–[37], [39], [44]–[46], [48]. It appears that newer studies were more likely to include a conflict of interest statement, which may reflect a recent change in reporting. Funding was acknowledged by most studies (18/20) and most received funding from academic or/and health research institutions. Two studies received funding from pharmaceutical companies – Lundbeck [43] and Pfizer [35] and one study acknowledged that Pfizer Italia provided the Italian version of PHQ-9 and gave the authors permission to use it [36].

Diagnostic test accuracy

Pooled sensitivity and specificity was calculated separately for the non-allegiant and allegiant studies. Pooled sensitivity for the allegiant studies of the PHQ-9 was 0.77 (95% CI = 0.70 – 0.84), pooled specificity was 0.94 (95% CI = 0.90 – 0.97), and the pooled diagnostic odds ratio was 64.40 (95% CI = 34.15 – 121.43). Heterogeneity was high (I^2 = 78.9%). Figure 1 represents the summary ROCs for this set of studies.

Figure 1. PHQ-9 algorithm scoring method summary ROC plot for the diagnosis of major depressive disorder in allegiant studies (Panel A) and non-allegiant studies (Panel B). Pooled sensitivity and specificity estimates using a bi-variate meta-analysis (*HSROC* hierarchical receiver-operating characteristic).

Pooled sensitivity for the non-allegiant studies was lower compared to the developer authored studies group at 0.48 (95% CI = 0.41 – 0.91), pooled specificity was the same at 0.94 (95% CI = 0.91 – 0.95). The pooled diagnostic odds ratio was approximately four times lower at 15.05 (95% CI = 11.03 – 20.52) (see figure 1). Heterogeneity was substantial at I^2 = 68.1 %.

The meta-regression analysis for algorithm studies with non-allegiant status as the predictor of the diagnostic odds ratio showed that non-allegiant status was a significant predictor of the diagnostic odds ratio ($p < 0.0001$) and explained a substantial amount of the observed heterogeneity (51.5%).

Quality assessment

The results of the quality assessment using QUADAS-2 are given in table 3 for the studies reporting on the diagnostic performance of the algorithm scoring method. In the patient selection domain, more non-allegiant studies (65%, 13/20) than allegiant (29%, 2/7) met the criterion for consecutive referrals. There were no marked differences on the other two criteria in this domain (avoid case-control design, avoid inappropriate exclusions). In the index test domain, the proportion of studies reporting that the PHQ-9 was conducted blind to the reference test was comparable between the two groups. There were differences in this domain for those studies using a translated version of the test. All non-English allegiant studies (5/5) used an appropriately translated version of the PHQ-9; whereas just over a half of the non-allegiant studies reported this (55%, 6/11). However, the majority of both sets of studies did not report details of psychometric properties of the translated version. For the reference test domain, nearly all studies in both groups were rated as using a reference test that would correctly classify the condition. While most allegiant studies reported that the reference test was interpreted blind to the PHQ-9 score (86%, 6/7), this was reported in only 60% (12/20) of the non-allegiant studies.

The two sets of studies that used translated versions of the reference test were broadly comparable. There was a slight indication that the allegiant studies were more likely to use an appropriately translated version of the reference test and report data on the psychometric properties of the translated version, though the numbers for the translated comparison are very low. There were, however, some more notable differences on the flow and timing domain. Most allegiant studies ensured that the time between the index and reference test was under two weeks (86%, 6/7) in comparison to 70% (14/20) of the non-allegiant studies. More allegiant studies met the criterion for 'all participants included in the analysis' (57%, 4/7) than non-allegiant studies (25%).

Summed items scoring method (cut-off point 10 or above)

Descriptive characteristics

Table 2 presents the sample characteristics of the thirty-one PHQ-9 validation studies that reported the psychometric properties of the PHQ-9 at cut-off point 10 or above. Five of these studies were co-authored by the original developers of the instrument or acknowledged collaboration [12], [23], [26], [49] or were co-authored by the first author of a previous study that had also been co-authored by one of the developers [28]. Twenty-six studies were conducted by independent researchers.

Three (60%, 3/5) allegiant studies [26], [28], [49] and eleven non-allegiant studies (42%, 11/26) [30]–[32], [34], [37], [38], [50]–[54] were conducted in hospital settings.

Three (60%, 3/5) allegiant studies[12], [26], [49] and thirteen non-allegiant studies (13/26) [30], [37], [38], [42], [48], [51]–[53], [55]–[59], were conducted in English.

The mean prevalence of major depressive disorder in the allegiant group was 13.2% (range 6.1% - 33.5%) and in the non-allegiant group was 16.1% (range 2.5% - 43.2%). The mean age of patients in the allegiant group studies was 48.1 (range 41.9 -61.0) and in the 26 non-allegiant studies that reported these data was 49.1 (range 23.0 – 78.0). The percentage of females in the allegiant studies that reported these data [12], [23], [26], [28] was 56.3% (range 28.6% – 67.8%) and in the non-allegiant group was 64.9 % (range 12% -100%).

Three allegiant studies used the self-reported mode of administration and two of them did not specify how the PHQ-9 was administered. In 9 non-allegiant studies (34%, 9/26) the PHQ-9 was administered by the researcher [30]–[32], [48], [56], [58]–[61]. All allegiant studies used SCID as a gold standard; the non-allegiant studies used a wider range of gold standards including SCAN, CIDI, MINI, CIS-R, C-DIS, though the SCID was used in half of the studies (50%, 13/26 studies).

Three allegiant studies (60%) did not include a conflict of interests statement [12], [23], [49]. Two of these studies [12], [23] acknowledged funding from Pfizer. None of the allegiant studies acknowledged collaboration or authorship of one of the developers of the PHQ-9.

Of the non-allegiant studies, thirteen (42%) did not include a conflict of interests statement [30]–[32], [37], [42], [46], [48], [53], [55], [60], [62]–[64]. Similar to the algorithm studies, the newer studies were more likely to include a conflict of interest statement. Funding was acknowledged by most studies (27/31) and most received funding from academic or/and health research institutions. One study [57] acknowledged that the last author involved in the development of one of the instruments (CORE-OM), 'but does not gain financially from its use'. One study [51] acknowledged funding from industry, AHA Pharmaceuticals Roundtable, but stated that 'the funding organisations had no role in the design or conduct of the study, collection, management, analysis or interpretation of data; or preparation, review or approval of the manuscript. Fine et al., 2013 disclosed that the last author had financial and consulting interests (Pfizer was not cited as one of them).

Diagnostic test accuracy

Pooled sensitivity of allegiant studies was 0.87 (95% CI = 0.77 – 0.93), pooled specificity was 0.87 (95% CI = 0.76 – 0.94), and the pooled diagnostic odds ratio was 49.31 (95% CI = 25.74 – 94.48) – see table 5. Heterogeneity was moderate (I^2 = 55.1%). Figure 2 represents the summary ROCs for this group.

Figure 2. PHQ-9 summed items scoring method at cut-off point 10 summary ROC plot for diagnosis of major depressive disorder in allegiant studies (panel A) and non-allegiant studies (panel B). Pooled sensitivity and specificity using a bi-variate meta-analysis (*HSROC* hierarchical receiver-operating characteristic).

Pooled sensitivity of non-allegiant studies was 0.76 (95% CI, 0.67 – 0.83), pooled specificity was 0.88 95% CI (0.85 – 0.91), and the pooled diagnostic odds ratio was 24.96 (95% CI 14.81 – 42.08), approximately half that of the allegiant studies (table 2). Heterogeneity was high at I^2 = 81.5 %. Figure 2 represents the summary ROCs for this group.

The meta-regression for the studies using a cut-off point of 10 or above with allegiance status of the predictor showed that allegiance status was a significant predictor of the diagnostic odds ratio (P = 0.015) and explained 19.0% of observed heterogeneity.

Quality assessment

The results of the quality assessment using the QUADAS-2 are given in table 4. For the patient selection domain, the two groups of studies were broadly comparable on two items (consecutive or random sample, avoid case-control design). However, all allegiant studies were rated as avoiding inappropriate exclusions (5/5) in contrast to 58% (15/26) of the non-allegiant studies.

On the index test domain, there were a number of differences between the two groups of studies. More of the non-allegiant studies (81%, 21/26) reported that the PHQ-9 was interpreted blind to the reference test compared to 60% (3/5) of the allegiant studies. All (5/5) allegiant studies were rated as pre-specifying the threshold on the PHQ-9 compared to 73% (19/26) of the non-allegiant studies. The two sets of studies were broadly comparable in terms of two items from the reference test domain (correctly classify target condition, reference test interpreted blind). Only one allegiant study used a translated version of the index test or reference test, so it is not possible to comment on differences between the two sets of studies in terms of these items from the index or reference test domains. For the flow and timing domain, the two groups of studies were broadly comparable for two of the criteria (interval of two weeks or less, all participants receive same reference test). However, fewer than half of the non-allegiant studies met the criterion for 'all participants included in the analysis' (42%, 11/26); whereas all allegiant studies met this criterion.

Discussion

This is to our knowledge the first systematic examination of a possible 'allegiance' or authorship effect in the validation of screening or case finding psychological instrument for a common mental health disorder. We reviewed diagnostic validation studies of the PHQ-9, a widely used depression screening-instrument. We found that allegiant studies reported higher sensitivity paired with similar specificity compared to non-allegiant studies. When entered as a covariate in meta-regression analyses, allegiance status was predictive of variation in the DOR for both the algorithm scoring method and the summed-item scoring method at a cut-off point of 10 or above.

Previous research has proposed several possible explanations for the allegiance effect [9]–[11]. One possibility is the advertent bias that may serve to inflate the performance of a test when evaluated by those who have developed it. However, before concluding that the differences are due to this, it is important to explore and rule out alternative explanations. First, it is possible that any observed differences are a result of differences in study characteristics of the two sets of studies (e.g., setting, clinical population). Secondly, differences in the methodological quality of the studies may also account for any differences. These possibilities are examined below.

Difference in study characteristics as potential alternative explanations

The two sets of studies were broadly comparable in terms of gender and the prevalence of depression, so these variables are unlikely to offer an explanation for the differences. While there were some indications from both sets of comparisons that the PHQ-9 may have been researcher-administered more often in the independent studies, it is not immediately clear how this would lead to lowered diagnostic performance.

The diagnostic meta-analyses of the PHQ-9 [13], [14] have shown that the sensitivity and DOR of the PHQ-9 tends to be lower in hospital settings for both algorithm and summed-item scoring methods. Whilst the fact that proportionally more non-allegiant algorithm studies were conducted in secondary care could explain the lower sensitivity and DOR values in the algorithm studies, in the studies that reported the cut-off point of or above this would not be the case as proportionally more allegiant studies were conducted in hospital settings.

Similarly, differences in the proportions of studies using translated versions of the PHQ-9 are also unlikely to offer an obvious explanation of the difference in diagnostic performance, because in the algorithm set of studies more of the allegiant studies used a translated version of the test, but the proportions were in the opposite direction for the studies using a cut off of 10 or above. We tested this by carrying out a sensitivity analysis restricting the sample to English studies and studies with adequate translation. The allegiance effect was still predictive of DOR variation between allegiance and non-allegiance studies variation in both algorithm ($p = 0.00$) and summed item scoring at cut-off point of 10 meta-analyses ($p = 0.02$).

A similar conclusion is also likely to apply to the age of the samples. There were more older adults studies in the non-allegiant than allegiant studies in the algorithm comparison. Depression could be more difficult to identify in older adults due to physical co-morbidities that may present with similar symptomatology to depression and could account for the lower diagnostic performance in the non-allegiant studies. However, the non-allegiant samples in the studies that reported the psychometric properties at cut-off point 10 or above had younger samples than the allegiant studies, so this would not support this interpretation.

The SCID was used as the gold standard in nearly all allegiant studies. The fact that some non-allegiant studies used other gold standards could potentially explain the poorer psychometric properties of the PHQ-9 in these studies. The SCID is often regarded as the most valid of the available semi-structured interviews used in depression diagnostic validity studies as the reference standard. If we assume that this is the case and, furthermore, that the PHQ-9 is an accurate method of screening for depression, then the PHQ-9 may be more likely to agree with the SCID

than other reference standards. However, when we carried out a sensitivity analysis restricting the sample to SCID only studies the allegiance effect was still predictive of DOR variation between allegiance and non-allegiance studies variation in both algorithm (p = 0.01) and summed item scoring at cut-off point of 10 reviews (p= 0.02).

Differences in methodological quality as potential alternative explanations

The quality of the studies was evaluated using the QUADAS-2. Although there were several potential methodological differences between the two groups of studies from the algorithm papers, not all of these offer obvious explanations of the observed differences and some are unlikely as explanations. For example, more allegiant studies ensured that the reference test was interpreted blind to the index test. This is unlikely to account for the observed differences, because a lack of blinding is typically associated with artificially increased diagnostic performance, which is in the opposite direction to the pattern of results observed here. The impact of some other differences is less clear-cut. For example, a higher number of the non-allegiant studies met the criterion for consecutive referrals. For this to provide an explanation of the of the observed differences, the non-consecutive nature of the referrals in the studies by those who had developed the PHQ-9 would need to have led to the over-inclusion of true positives or under-inclusion of false negatives given that these studies tended to report higher sensitivity relative to the non-allegiant studies (and vice versa for the independent studies). It is not immediately obvious how this would occur. The allegiant studies were more likely to have met the criterion of 'included all participants in the analysis'. It is possible that the greater loss of participants from the non-allegiant studies may have artificially reduced the observed diagnostic accuracy, though, again, it is not immediately obvious how this would have affected the true positive and false negative rates. Although there is not an obvious explanation of how these differences in methodological quality could account for the observed differences in diagnostic performance, it is important to recognise that they cannot on that basis be ruled out.

There are, however, two differences in methodological quality among the algorithm studies that are clearer potential alternative explanations. The higher rate of appropriate translations among the allegiant studies is potentially important, because lower diagnostic estimates may be expected from studies that have poorly translated versions of the index test. In the flow and timing domain, more allegiant studies ensured that there was a less than two-week interval between the index and reference test. This is consistent with lower diagnostic performance in the non-allegiant studies: as the interval increases it is likely that depression status may change and this would lead to lower levels of agreement between the index test and the reference test.

There were also differences on some quality assessment items between the two sets of studies in the summed item scoring method comparison. The threshold was reported as pre-specified in all allegiant studies in contrast to approximately three quarters of the non-allegiant studies. On the face of it, this is unlikely to explain the observed differences, because the use of a pre-specified cut-off point is likely to be associated with lower not higher diagnostic test performance. One possibility, however, is that studies that performed poorly at this cut-off point were less likely to be reported by those who had developed the measure. As discussed in more detail in the limitations section, we were unable to explore this possibility through the use of formal tests for publication bias.

All allegiant studies avoided inappropriate exclusions compared to approximately half of the non-allegiant studies. While this is a potential alternative explanation of the differences it is not immediately obvious how this would explain the differences in diagnostic performance between the two sets of studies. Fewer than half of the non-allegiant studies met the criterion for 'all participants included in the analysis', in contrast to all of the allegiant studies met this criterion, but again this difference should usually work against the inclusive studies, not those

excluding cases. More of the non-allegiant studies reported that the PHQ-9 was interpreted blind to the reference test. This does offer a potential explanation, because the absence of blinding may artificially inflate diagnostic accuracy.

Limitations

The results of this review need to be viewed in the light of the limitations of the primary studies that contributed to the review and the review itself. An important consideration is to establish whether any observed differences between the diagnostic performance of the non-allegiant and allegiant studies are better accounted for by study characteristic or methodological differences. Caution, however, is needed in interpreting any differences, because of the small number of allegiant studies in both the algorithm and cut-off 10 or above comparisons. The small number of allegiant studies also meant that we were also unable to explore the potential role of publication bias in the non-allegiant and allegiant studies. At least 10 studies are required to use standard methods of examining publication bias, but the number of allegiant studies in both the algorithm and cut-off 10 or above comparisons were fewer than this. Papers published from August 2013 onwards are not covered in the literature search used and so it potentially misses some more recent studies that would be eligible for inclusion although it is unlikely that many, if any, new allegiant studies have been published since.

Conclusions and implications for further research.

The aims of the review was to investigate whether an allegiance effect is found that leads to an increased diagnostic performance in diagnostic validation studies that were conducted by teams connected to the original developers of the PHQ-9. Our analyses showed that diagnostic studies conducted by independent/non-allegiant researchers had lower sensitivity paired with similar specificity compared to studies that were classified as allegiant. This conclusion held for both the algorithm and cut-off 10 or above studies. We explored a range of possible alternative explanations for the observed allegiance effect including both differences in study characteristics and study quality. A number of potential differences were found, though for some of these it is not clear how they would necessarily account for the observed differences. However, there were a number of differences that offered potential alternative explanations unconnected to allegiance effects. In the algorithm studies, the studies rated as allegiant were also more likely to use an appropriate translation of the PHQ-9 and were also more likely to ensure that the index and reference test were conducted within two weeks of each other, both of which may be associated with an improvement in observed diagnostic performance of an instrument. The majority of studies in both meta-analyses did not provide clear statements about potential conflict of interest and/or funding, however the newer studies were more likely to provide such statements, which may reflect increasing transparency in this area of research.

We cannot, therefore, conclude that allegiance effects are present in studies examining the diagnostic performance of the PHQ-9; but nor can we rule them out. Conflicts of interest are an important area of investigation in medical and behavioural research, particularly due to concerns about trial results being influenced by industry sponsorship. Future diagnostic validity in this area should as a matter of routine present clear statements about potential conflicts of interest and funding, particularly relating to the development of the instrument under evaluation. Future meta-analyses of diagnostic validation studies of psychological measures should routinely evaluate the impact of researcher allegiance in the primary studies examined in the meta-analysis.

Contributors LM led on all stages of the review and is the guarantor. We used an established database of diagnostic validation studies of the PHQ-9 [13], [14] SG provided expert advice on methodology and approaches to assessment of the evidence base. AM carried out the literature searches, screened the studies, extracted data and assessed the quality of the included studies for one of the systematic reviews (Moriarty et al., 2015) . LM carried out the literature searches, screened the studies, extracted data and assessed the quality of the included studies for the other systematic review (Manea et al., 2015), analysed the data for both systematic reviews and drafted the report. JB was involved in the development of the study, wrote the introduction section of the review and contributed to the production of the final report. DM supervised the quality assessment, methodology and approaches to evidence synthesis, provided senior advice and support throughout and contributed to the production of the final report. All parties were involved in drafting and/or commenting on the report.

Competing interests None declared.

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Table 1: Descriptive characteristics of algorithm studies (Manea et al., 2014)					
Study	**Sample characteristics (Country, setting, age, sex)**	**Sample size and % depressed**	**PHQ-9 characteristics**	**Diagnostic standard**	**a) Conflict of interest (COI) declaration b) Funding c) Relationship with original developers**
Diez-Quevedo et al. (2001)	Country: Spain Setting: Medical and surgical tertiary hospitals Age (yrs): M=43 (SD=14.2) Female: 45.6%	N = 1003 Depressed: 8.2%	Administration: Self-report Language: Spanish	DSM-III-R SCID	a) No COI declaration b) Funding acknowledged (academic institutions) c) Not acknowledged
Gräfe et al. (2004)	Country: Germany Setting: psychosomatic walk-in clinics and family practices Age (yrs): M = 41.9 (SD = 13.8) Female: 67.8%	N = 528 Depressed: 29.2% psychosomatic patients; 6.16% medical patients	Language: German Administration: self-report	DSM-IV SCID	a) No COI declaration b) Acknowledged funding from Pfizer c) Not acknowledged

Lowe et al. (2004)	Country: Germany Setting: Outpatient clinics and family practices Age (yrs): M = 41.7 (SD = 13.8) Female: 67.1%	N = 501 Depressed: 13.2%	Administration: Self-report Language: German	DSM–IV SCID	a) COI declaration 'This study was supported by unrestricted restricted grants from Pfizer Germany and from the medical faculty of the University of Heidelberg Germany, and there are no COI.' b) Acknowledged funding from Pfizer and academic institution c) Not acknowledged
Muramatsu et al. (2007)	Country: Japan Setting: Primary care and general hospital Age (yrs): M = 43.3 (SD = 16.4) Female: 59.5%	N = 131 Depressed: 28.2%	Administration: Self-report Language: Japanese	DSM–IV MINI	a) No COI declaration b) Acknowledged funding from Pfizer c) Acknowledged one of the developers of the PHQ-9: 'The authors acknowledge Dr R L Spitzer'
Navinés et al. (2012)	Country: Spain Setting: General hospital (patients with chronic HCV) Age (yrs): M = 43.4 (SD = 10.2) Female: 28.6%	N = 500 Depressed: 6.4%	Administration: Self-report Language: Spanish	DSM–IV SCID	a) All authors declared that they had no COI. b) Role of funding source declared c) Not acknowledged

Spitzer et al. (1999)	Country: US Setting: Primary care Age (yrs): M = 46 (SD = 17.2) Female: 66%	N = 3000 (585 received SCID) Depressed: 10%	Administration: Self-report Language: English	DSM-III-R SCID	a) No COI declaration b) Acknowledged funding from Pfizer. 'Drs Spitzer and Williams receive honoraria and consulting money from Pfizer Inc, which has supported this work.' c) N/A
Thekkumpurath et al. (2010)	Country: UK Setting: Hospital (cancer patients) Age (yrs): M = 61 Female: 63%	N = 782 Depressed: 6.3% (of the whole sample)	Administration: Not stated Language: English	DSM-IV SCID	a) COI declaration: 'Supported by Cancer Research UK' b) As in a) c) Not acknowledged
Ayalon et al. (2010)	Country: Israel Age (yrs): M = 75 (SD = 8.1) Female: 40.5 %	N = 153 Depressed: 3.9 %	Administration: Researcher administered Language: Hebrew	DSM-IV SCID	a) COI declaration: 'The project was funded by an Investigator's Initiated Research Grant from Lundbeck International given to Dr Liat Ayalon. Lundbeck International had no other involvement in the project concept of design or in this paper. Per Bech has occasionally over the past 3 years until August 2008 received funding from and has been speaker or member of advisory boards for pharmaceutical companies with an interest in the drug treatment of affective disorders (Astra-Zeneca, Lilly, H. Lundbeck A/S, Lundbeck Foundation and Organon). ' b) Acknowledged funding from Lundbeck International

Eack et al. (2006)	Country: US Setting: Community mental health centers for children Age (yrs): M = 39.20 (SD 9.63) Female: 100%	N = 50 Depressed: 28%	Administration: Self-report Language: English	DSM-IV SCID	a) No COI declaration b) Funding acknowledged (academic /health research institutions)
Fann et al. (2005)	Country: US Setting: Trauma hospital (inpatients with traumatic brain injury) Age (yrs): M = 42 (SD=17.9) Female: 29.1%	N = 135 Depressed: 16.3%	Administration: Telephone-administered Language: English	DSM-IV SCID	a) No COI declaration b) Funding acknowledged (academic institutions)

Gelaye et al. (2011)	Country: Ethiopia Setting: General hospital Age (yrs): 34.9 (SD=11.6) Female: 63.1 %	N = 363 Depressed: 12.6%	Administration: Researcher-administered Language: Amharic	DSM-IV SCAN	a) No COI declaration b) Funding acknowledged (academic /health research institutions)
Gjerdingen et al. (2009)	Country: US Setting: Community Age (yrs): M = 29.3 Female: 100%	N = 438 Depressed: 4.6%	Administration: Telephone or self-report Language: English	DSM-IV SCID	a) No COI declaration b) Funding acknowledged (academic /health research institutions)
Henkel et al. (2004)	Country: Germany Setting: primary care Age (yrs): not reported Female: 74%	N = 448 Depressed: 10%	Administration: self-report Language: German	DSM-IV CIDI	a) No COI declaration b) Funding acknowledged (academic /health research institutions)

Hyphantis et al. (2011)	Country: Greece Setting: Hospital – rheumatology patients Age (yrs): M = 54.2 (SD = 13.5) Female: 74%	N = 213 Depressed: 32.4%	Administration: Researcher administered Language: Greek	DSM-IV MINI	a) No COI declaration b) No funding acknowledgement
Inagaki et al. (2013)	Country: Japan Setting: General hospital Age whole sample (yrs): M = 73.5 (SD = 12.3) Female: 59.3%	N = 104 out of 511 received MINI Depressed: 7.4%	Administration: Researcher administered Language: Japanese	DSM-IV MINI	a) COI declaration: 'The authors declare that they have no competing interests.' b) Funding acknowledged (academic /health research institutions)
Khamseh et al. (2011)	Country: Iran Setting: Diabetes clinic Age (yrs): M = 56.17 (SD = 9.60) Female: 51.9%	N = 185 Depressed: 43.2%	Administration: Self report Language: Persian	DSM-IV SCID	a) COI declaration: The authors declared no competing interests b) Funding acknowledged (academic /health research institutions)

Lamers et al. (2008)	Country: Netherlands Setting: Primary care (elderly) Age (yrs): M = 71.4 (SD = 6.90) Female: 48.2%	N = 713 Depressed: 10.7%	Administration: Self report Language: Dutch	DSM-IV MINI	a) No COI declaration b) Funding acknowledged (academic /health research institutions)
Lotrakul et al. (2008)	Country: Thailand Setting: Primary care Age (yrs): M = 45.0 (SD = 14.30) Female: 73.7%	N = 279 Depressed: 6.8%	Administration: Self report Language: Thai	DSM-IV MINI	a) No COI declaration b) Funding acknowledged (academic /health research institutions)
Persoons et al. (2003)	Country: Belgium Setting: Hospital (otolaryngology patients) Age (yrs): M = 48.2 (SD = 12.9) Female: 65.6%	N = 268 (97 received MINI) Depressed: 16.5%	Administration: Self-report Language: Dutch	DSM-IV MINI	a) No COI declaration b) Funding acknowledged (academic /health research institutions) and Pfizer Belgium

Picardi et al. (2005)	Country: Italy Setting: Hospital (dermatology inpatients) Age (yrs): M = 37.5 Female: 56%	N = 141 Depressed: 8.5%	Administration: Self-report Language: Italian	DSM-IV SCID	a) No COI declaration b) Funding acknowledged (academic /health research institutions). Acknowledged Pfizer Italia SRL for providing the Italian version of the PHQ-9 and for permission to use it.
Stafford et al. (2007)	Country: Australia Setting: Hospital (cardiology patients) Age (yrs): M = 64.1 (SD = 10.3) Female: 66%	N = 193 Depressed: 18%	Administration: Self-report Language: English	DSM–IV MINI	a) No COI declaration b) Funding acknowledged (academic/health research institutions)
Thombs et al. (2008)	Country: US Setting: Hospital (outpatients with coronary heart disease) Age (yrs): M = 67 (SD = 11) Female: 18%	N = 1024 Depressed: 22%	Administration: Not stated Language: English	DSM C-DIS	a) COI declaration “None disclosed” b) Funding acknowledged (academic/health research institutions)

Thompson et al. (2010)	Country: US Setting: Patients with Parkinson Disease Age (yrs): 72.5 (SD = 9.6) Female: 42%	N = 214 Depressed: 14%	Administration: Self administered Language: English	DSM-IV SCID	a) No COI declaration b) Funding acknowledged (academic/health research institutions)
Turner et al. (2012)	Country: Australia Setting: Stroke patients Age (yrs): 66.7 (SD = 13.1) Female: 47.2%	N = 72 Depressed: 18%	Administration: Self administered Language: English	DSM-IV SCID	a) COI declaration: Disclosures 'None'. b) Funding acknowledged (academic/health research institutions)

van Steenbergen-Weijenburg (2010)	Country: Netherlands Setting: Diabetes patients Age (yrs): M = 61.8 (SD = 13.6) Female: 48.7%	N = 197 Depressed: 18.8%	Administration: Self administered Language: Dutch	DSM-IV SCID	a) COI declaration: 'The authors declare that they have no competing interests'. b) Funding acknowledged (academic/health research institutions) – 'this had no influence on the content of this article'.
Zuitthoff et al. (2010)	Country: Netherlands Setting: Primary care Age (yrs): M = 51 (sd = 16.7) Female: 63%	N = 1338 Depressed: 13%	Administration: Self-report Language: Dutch	DSM-IV CIDI	a) COI declaration 'The authors declare that they have no competing interests.' b) Funding acknowledged (academic/health research institutions).

Table 2: Descriptive characteristics of the summed items scoring method studies cut-off point 10 (Moriarty et al, 2015)

Study	Sample characteristics	Sample size and % MDD	PHQ-9 characteristics	Diagnostic standard	Conflict of interest (COI) declaration Funding c) Relationship with original developers
13. Gräfe et al. (2004)	Country: Germany Setting: psychosomatic walk-in clinics and family practices Mean age: 41.9 (SD = 13.8) Female: 67.8%	N = 528 Depressed: 29.2% psychosomatic patients; 6.16% medical patients	Administration: self-report Language: German Cut-offs: 10 to 14	DSM-IV SCID	No COI declaration Acknowledged funding from Pfizer Not acknowledged
16. Kroenke et al. (2001)	Country: USA Setting: Primary care Mean age: 46 (SD=17) Female: 66%	N = 580 7.1% MDD	Administration: Self-report Language: English Cut-offs: 9 to 15	DSM-IV SCID	a) No COI declaration b) Acknowledged funding from Pfizer c) N/A
22. Navinés et al. (2012)	Country: Spain Setting: General hospital (patients with chronic HCV) Mean age: 43.4 (SD = 10.2) Female: 28.6%	N = 500 6.4% MDD	Administration: Self-report Language: Spanish Cut-offs: 10	DSM–IV SCID	`a) All authors declared that they had no COI. b) Role of funding source declared c) Not acknowledged
29. Thekkumpurath et al. (2010)	Country: UK Setting: Hospital (cancer patients) Mean age: 61 Female: 63%	N = 782 6.3% MDD (of the whole sample)	Administration: Not stated Language: English Cut-offs: 5 to 10	DSM-IV SCID	c) COI declaration: 'Supported by Cancer Research UK' d) As in a) e) Not acknowledged
33. Williams et al. (2005)	Country: USA	N = 316	Administration: Unclear	DSM-IV SCID	a) No COI declaration b) Funding

	Setting: Secondary care (Post-stroke) Mean age: Unclear Female: Unclear	33.5% MDD	Language: English Cut-offs: 10		acknowledged (academic institutions) c) Not acknowledged

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1. Adewuya et al. (2006)	Country: Nigeria Setting: community (students) Mean age: 24.8 (15-40) Female: 41.2%	N = 512 2.5% MDD	Administration: Self-report Language: English Cut-offs: 8 to 12	DSM-IV MINI	a) No COI declaration b) No funding declaration
2. Arroll et al. (2010)	Country: New Zealand Setting: Primary care Mean age: 49 (17-99) Female: 61%	N = 2642 6.2% MDD	Administration: Not stated Language: English Cut-offs: 8,10,12,15	DSM-IV SCID	a) No COI declaration b) Funding acknowledged (academic /health research institutions)
3. Azah et al. (2005)	Country: Malaysia Setting: Primary care Mean age: 38.7 (18-79) Female: 61.7%	N = 180 16.6% MDD	Administration: Self-report Language: Malay Cut-offs: 5 to 12	DSM-IV CIDI	b) No COI declaration c) Funding acknowledged (academic /health research institutions)
4. Chagas et al. (2013)	Country: Brazil	N = 84	Administration: self-report	DSM-IV SCID	a) COI declaration "None declared"

	Setting: Secondary care Mean age: Not stated Female: 52.7%	25.5% MDD	Language: Brazilian Cut-offs: 7 to 10		b) Funding acknowledged (academic/health research institutions)
6. de Lima Osorio et al. (2009)	Country: Brazil Setting: Primary care Mean age: Unclear Female: 100%	N = 177 34% MDD	Administration: research assistants Language: Brazilian Portuguese Cut-offs: 10 to 15	DSM-IV SCID	a) No COI declaration b) Funding acknowledged (academic institutions)
7. Elderon et al. (2011)	Country: USA Setting: Secondary care Mean age: Unclear Female: 18%	N = 1022 18.3% MDD	Administration: self-report Language: English Cut-offs: 10	C-DIS	a) COI declaration – 'No disclosures' b) Funding acknowledged (academic institutions and industry – AHA Pharmaceuticals Roundtable) – 'The funding organisations had no role in the design or conduct of the study, collection, management, analysis or interpretation of data; or preparation, review or approval of the manuscript.'
8. Fann et al. (2005)	Country: US Setting: Trauma hospital (inpatients with traumatic	N = 135 16.3% MDD	Administration: Telephone-administered Language: English	DSM-IV SCID	b) No COI declaration c) Funding acknowledged (academic

	brain injury) Mean age: 42 (SD=17.9) Female: 29.1%		Cut-offs: 10		institutions)
9. Fine et al. (2013)	Country: USA Setting: Primary care (Ohio Army National Guard) Mean age: 31 (17-60) Female: 12%	N = 498 21.5% MDD	Administration: Telephone-administered Language: English Cut-offs: 10,15	DSM-IV SCID-I	a) COI – last author disclosed financial and consulting interests (Pfizer not one of them). All other authors declared that they have no COI. b) Funding acknowledged – DoD Medical Research. ‘’The sponsor had no role in study design, data collection, analysis, interpretation of results, report writing or manuscript submission.
10. Gelaye et al. (2013)	Country: Ethiopia Setting: General hospital Mean age: 34.9 (SD=11.6) Female: 63.1 %	N = 363 12.6% MDD	Administration: Researcher-administered Language: Amharic Cut-offs: 9 to 11	DSM-IV SCAN	c) No COI declaration d) Funding acknowledged (academic /health research institutions)
11. Gilbody et al.	Country: UK	N = 96	Administration: Not	DSM-IV	a) COI declaration –

(2007)	Setting: Primary care Mean age: 42.5 (SD 13.6) Female: 77%	37.5 MDD	stated Language: English Cut-offs: 9 to 13	SCID	last author involved in the development of one of the instruments (CORE-OM), 'but does not gain financially from its use. b) Funding acknowledged (academic /health research institutions)
12. Gjerdingen et al. (2009)	Country: USA Setting: Community Mean age: 29.3 Female: 100%	N = 438 4.6% MDD	Administration: Telephone or self-report Language: English Cut-offs: 10	DSM-IV SCID	c) No COI declaration d) Funding acknowledged (academic /health research institutions)
14. Hyphantis et al. (2011)	Country: Greece Setting: Hospital – rheumatology patients Mean age: 54.2 (SD = 13.5) Female: 74%	N = 213 32.4% MDD	Administration: Researcher administered Language: Greek Cut-offs: 4 to 16	DSM-IV MINI	c) No COI declaration d) No funding acknowledgement
15. Khamseh et al. (2011)	Country: Iran Setting: Outpatient diabetic clinic Mean age: 56.1 (SD=9.6)	N = 185 43.2% MDD	Administration: Self-report Language: Persian Cut-offs: 10,13	DSM-IV SCID	c) COI declaration: The authors declared no competing interests d) Funding acknowledged (academic /health

	Female: 51.8%				research institutions)
19. Liu et al. (2011)	Country: Taiwan Setting: Primary care Mean age: Not specified Female: 60.9%	N = 1532 3.3% MDD	Administration: Self-report Language: Chinese version Cut-offs: 9 to 11	SCAN	a) a) No COI declaration b) Funding acknowledged (academic /health research institutions)
20. Lotrakul et al. (2008)	Country: Thailand Setting: Primary care Mean age: 45.0 (SD = 14.30) Female: 73.7%	N = 279 6.8% MDD	Administration: Self report Language: Thai Cut-offs: 7 to 15	DSM-IV MINI	c) No COI declaration d) Funding acknowledged (academic /health research institutions)
23. Patel et al. (2008)	Country: India Setting: Primary care Mean age: 37.5 (18-83) Female: 56.4%	N = 299 4.3% MDD	Administration: Face-to-face interview Language: Not specified Cut-offs: 7 to 15	CIS-R	a) COI declaration – No Declaration of Interest b) Funding acknowledged (academic /health research institutions)
24. Phelan et al. (2010)	Country: USA Setting: Primary care (elderly) Mean age: 78 (SD=7) Female: 62%	N = 71 12% MDD	Administration: Research assistant Language: English Cut-offs: 8 to 12	DSM-IV SCID	a) COI declaration – No competing interests b) Funding acknowledged (academic /health research institutions) . 'The funder had no role in the study design, methods,

					data collection, analysis or interpretation of data, nor any role in the preparation of the manuscript or decision to submit the manuscript for publication.
25. Rooney et al. (2013)	Country: UK Setting: Secondary care (glioma) Mean age: 54.2 (SD=12.3) Female: 42.6%	N = 129 13.5% MDD	Administration: Self-report Language: English Cut-offs: 8 to 11	DSM-IV SCID	a) COI declaration "The authors declare that they have no COI" b) Funding acknowledged (academic/health research institutions)
26. Sherina et al. (2012)	Country: Malaysia Setting: Primary care Mean age: 30.9 (18-81) Female: 100%	N= 146 21.2% MDD	Administration: Self-report Language: Malay Cut-offs: 10	CIDI	a) COI declaration "The authors declare that they have no competing interests" b) Funding acknowledged (academic/health research institutions)
27. Sidebottom et al. (2012)	Country: USA Setting: Community (prenatal) Mean age: 23 (SD=5.5) Female: 100%	N = 745 3.6% MDD	Administration: Interview Language: English Cut-offs: 10	DSM-IV SCID	b) COI declaration "The authors declare that they have no financial COI" b) Funding acknowledged (academic/health research institutions)
28. Stafford et al. (2007)	Country: Australia Setting: Secondary care (cardiac procedures)	N = 193 18.1% MDD	Administration: Self-report Language: English	DSM-IV MINI	b) No COI declaration c) Funding acknowledged (academic/health

	Mean age: 64.14 (38-91) Female: 19.2%		Cut-offs: 10		research institutions)
30. Thombs et al. (2008)	Country: US Setting: Hospital (outpatients with coronary heart disease) Mean age: 67 (SD = 11) Female: 18%	N = 1024 22% MDD	Administration: Not stated Language: English Cut-offs: 7 to 10	DSM C-DIS	b) COI declaration "None disclosed" b) Funding acknowledged (academic/health research institutions)
32. Watnick et al. (2005)	Country: USA Setting: Secondary care (dialysis) Mean age: 63 (SD=15) Female: 32.3%	N = 62 19% MDD	Administration: Self-report Language: English Cut-offs: 10	DSM-IV SCID	b) No COI declaration c) Funding acknowledged (academic/health research institutions)
34. Wittkampf et al. (2009)	Country: Netherlands Setting: Primary care Mean age: 49.8 Female: 66.7%	N = 664 12.3% MDD	Administration: Self-report Language: Not specified Cut-offs: 10 and 15	DSM-IV SCIDI	No COI declaration b) Funding acknowledged (academic/health research institutions)
35. Zhang et al. (2013)	Country: Hong Kong Setting: Secondary care (diabetic outpatients) Mean age: 55.1 (SD=9.5)	N = 99 23.2% MDD	Administration: Self-report Language: Chinese version Cut-offs: 15	DSM-IV MINI	COI declaration – last author acknowledged financial COI. The other authors declare that they have no competing interests.) Funding acknowledged

	Female: 40.8%				(academic/health research institutions)
36. Zuithoff et al. (2010)	Country: Netherlands Setting: Primary care Age (yrs): M = 51 (sd = 16.7) Female: 63%	N = 1338 Depressed: 13%	Administration: Self-report Language: Dutch	DSM-IV CIDI	b) COI declaration "The authors declare that they have no competing interests. b) Funding acknowledged (academic/health research institutions)

Table 3: Quality assessment of included studies in the algorithm meta-analysis (Manea et al., 2014)

Study	Patient selection: Consecutive or random sample	Patient selection: Avoid case-control / avoid artificially inflated base rate	Patient selection: Avoided inappropriate exclusions	Patient selection: Overall risk of bias	Index test: PHQ-9 interpreted blind to reference test	Index test: If translated, appropriate translation	Index test: If translated, psychometric properties reported	Index test: Overall risk of bias
Allegiant studies								
Diez-Quevedo et al. (2001)	×	✓	×	High	?	✓	✓	Unclear
Gräfe et al. (2004)	✓	✓	✓	Low	?	✓	✓	Unclear

Lowe et al. (2004)	×	✓	✓	High	✓	✓	✓	Low
Muramatsu et al. (2007)	?	✓	?	Unclear	✓	✓	?	Unclear
Navines et al. (2012)	✓	✓	✓	Low	✓	✓	?	Unclear
Spitzer et al. (1999)	×	✓	✓	High	✓	n/a	n/a	Low
Thekkumpurath et al. (2010)	×	×	✓	High	✓	n/a	n/a	Low
Non-allegiant studies								
Arroll et al. (2010)	✓	✓	✓	Low	✓	n/a	n/a	Low
Ayalon et al. (2010)	?	✓	✓	Unclear	?	✓	?	Unclear
Eack et al. (2006)	?	✓	?	Unclear	?	n/a	n/a	Unclear
Fann et al. (2005)	✓	×	×	High	✓	n/a	n/a	Low
Gelaye et al. (2013)	?	×	?	High	✓	✓	?	Unclear
Gjerdingen et	✓	✓	✓	Low	?	n/a	n/a	Unclear

al. (2009)								
Henkel et al. (2004)	✓	✓	✓	Low	?	n/a	n/a	Unclear
Hyphantis et al. (2011)	✓	✓	×	High	✓	?	?	Unclear
Inagaki et al. (2013)	✓	×	✓	High	✓	?	?	Unclear
Khamseh et al. (2011)	✓	✓	?	Unclear	✓	✓	?	Unclear
Lamers et al (2008)	✓	×	×	High	✓	?	?	Unclear
Lotrakul et al. (2008)	×	✓	?	High	✓	✓	?	Unclear
Persoons et al. (2003)	✓	✓	✓	Low	✓	✓	n/a	Low
Picardi et al. (2005)	✓	✓	✓	Low	✓	?	?	Unclear
Stafford et al. (2007)	✓	✓	✓	Low	✓	n/a	n/a	Low
Thombs et al. (2008)	×	✓	?	Unclear	?	n/a	n/a	Unclear
Thomspon et	?	✓	✓	Unclear	?	n/a	n/a	Unclear

al. (2011)								
Turner et al. (2012)	✓	✓	✓	Low	✓	n/a	n/a	Low
Van Steenbergen-Wijenburg (2010)	?	✓	✓	Unclear	?	?	?	Unclear
Zuithoff et al. (2010)	✓	✓	✓	Low	✓	✓	?	Unclear

✓ = criterion met; × = criterion not met; ? = insufficient information to code whether criterion met; n/a = not applicable

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Table 3: Quality assessment of included studies in the algorithm meta-analysis (Manea et al., 2014) (continued)

Study	Reference test: Reference test correctly classifies target condition	Reference test: Reference test interpreted blind to PHQ-9	Reference test: If translated, appropriate translation	Reference test: If translated, psychometric properties reported	Reference test: Overall risk of bias	Flow / timing: Interval of two weeks or less	Flow / timing: All participants receive same reference test	Flow / timing: All participants included in analysis?	Flow / timing: Overall risk of bias
Allegiant studies									
Diez-Quevedo et al. (2001)	✓	✓	✓	?	Unclear	✓	✓	✓	Low

Gräfe et al. (2004)	✓	?	n/a	n/a	Unclear	✓	✓	✓	Low
Lowe et al. (2004)	✓	✓	n/a	n/a	Low	✓	✓	✓	Low
Muramatsu et al. (2007)	✓	✓	✓	✓	Low	✓	✓	?	Unclear
Navines et al. (2012)	✓	✓	?	?	Unclear	✓	✓	✓	Low
Spitzer et al. (1999)	✓	✓	n/a	n/a	Low	✓	✓	×	High
Thekkumpurath et al. (2010)	✓	✓	n/a	n/a	Low	?	✓	×	High
Non-allegiant studies									
Arroll et al. (2010)	✓	✓	n/a	n/a	Low	✓	✓	✓	Low
Ayalon et al. (2010)	✓	?	✓	?	Unclear	?	✓	✓	Unclear
Eack et al. (2006)	✓	?	n/a	n/a	Unclear	?	✓	?	Unclear
Fann et al. (2005)	✓	?	n/a	n/a	Unclear	✓	✓	×	High
Gelaye et al.	✓	✓	✓	✓	Low	✓	✓	×	High

(2013)									
Gjerdingen et al. (2009)	✓	?	n/a	n/a	Unclear	✓	✓	×	High
Henkel et al. (2004)	✓	?	n/a	n/a	Unclear	✓	✓	×	High
Hyphantis et al. (2011)	✓	✓	?	?	Unclear	✓	✓	×	High
Inagaki et el. (2013)	✓	✓	✓	?	Unclear	✓	✓	×	High
Khamseh et al (2011)	✓	✓	✓	?	Unclear	✓	✓	?	Unclear
Lamers et al. (2008)	✓	✓	?	?	Unclear	?	✓	×	High
Lotrakul et al. (2008)	✓	✓	✓	✓	Low	?	✓	×	High
Persoons et al. (2003)	✓	✓	?	?	Unclear	✓	✓	✓	Low
Picardi et al. (2005)	✓	✓	✓	?	Unclear	✓	✓	×	High
Stafford et al. (2007)	✓	✓	n/a	n/a	Low	✓	✓	×	High
Thombs et al.	?	✓	n/a	n/a	Unclear	✓	✓	✓	Low

Table 4: Quality assessment of included studies in the summed item scoring method cut-off point 10 meta-analysis (Moriarty et al., 2015)

(2008)									
Thompson et al. (2011)	✓	?	n/a	n/a	Unclear	✓	✓	×	High
Turner et al. (2012)	✓	?	n/a	n/a	Unclear	?	✓	×	High
Van Steenbergen-Wijenburg (2010)	✓	×	?	?	High	✓	✓	×	High
Zuithoff et al. (2010)	✓	✓	?	?	Unclear	?	✓	✓	Unclear

✓ = criterion met; × = criterion not met; ? = insufficient information to code whether criterion met;
n/a = not applicable

Study	Patient selection: Consecutive or random sample	Patient selection: Avoid case-control / avoid artificially inflated base rate	Patient selection: Avoided inappropriate exclusions	Patient selection: Overall risk of bias	Index test: PHQ-9 interpreted blind to reference test	Index test: Was a threshold pre-specified?	Index test: If translated, appropriate translation	Index test: If translated, psychometric properties reported	Index test: Overall risk of bias
Allegiant studies									
13. Gräfe et al. (2004)	✓	✓	✓	Low	?	✓	✓	✓	Unclear
16. Kroenke et al. (2011)	✓	✓	✓	Low	✓	✓	n/a	n/a	Low
22. Navinés et al. (2012)	✓	✓	✓	Low	✓	✓	✓	?	Unclear
29. Thekkumpurath et al. (2010)	✗	✗	✓	High	✓	✓	n/a	n/a	Low
33. Williams et al. (2005)	✓	✓	✓	Low	?	✓	n/a	n/a	Unclear
Non-allegiant studies									
1. Adewuya et	✓	✓	✗	Unclear	✓	✓	n/a	n/a	Low

al. (2006)									
2. Arroll et al. (2010)	✓	✓	✓	Low	✓	✓	n/a	n/a	Low
3. Azah et al. (2005)	✓	✗	?	High	✓	✓	✓	✓	Low
4. Chagas et al. (2013)	✓	✓	✓	Low	✓	✓	✓	✓	Low
6. de Lima Osorio et al. (2009)	✓	✗	✓	High	?	✗	n/a	n/a	High
7. Elderon et al. (2011)	✓	✓	✓	Low	✓	✓	n/a	n/a	Low
8. Fann et al. (2005)	✓	✗	✗	High	✓	✓	n/a	n/a	Low
9. Fine et al. (2013)	✓	✓	✓	Low	?	✓	n/a	n/a	Unclear
10. Gelaye et al. (2013)	?	✗	?	High	✓	✗	✓	?	High
11. Gilbody et al.	?	✓	?	Unclear	✓	✓	n/a	n/a	Low

(2007)									
12. Gjerdingen et al. (2009)	✓	✓	✓	Low	?	✓	n/a	n/a	Unclear
14. Hyphantis et al. (2011)	✓	✗	✓	High	✓	✓	?	?	Unclear
15. Khamseh et al. (2011)	✓	✓	?	Unclear	✓	✓	✓	?	Unclear
19. Liu et al. (2011)	✓	✓	?	Unclear	✓	✗	✓	?	High
20. Lotrakul et al. (2008)	✗	✓	?	Unclear	✓	✓	✓	?	Unclear
23. Patel et al. (2008)	✓	✓	✓	Low	✓	✓	?	?	Unclear
24. Phelan et al. (2010)	✗	✓	✓	High	✓	✗	n/a	n/a	High
25. Rooney et al. (2013)	✓	✓	✓	Low	?	✗	n/a	n/a	High
26. Sherina et al.	✓	✓	✗	High	✓	✓	✓	✓	Low

(2012)									
27. Sidebottom et al. (2012)	✓	✓	✓	Low	✓	✓	n/a	n/a	Low
28. Stafford et al. (2007)	✓	✓	✓	Low	✓	✓	n/a	n/a	Low
30. Thombs et al. (2008)	✗	✓	?	High	✓	?	n/a	n/a	Unclear
32. Watnick et al. (2005)	?	✗	✓	High	✓	✓	n/a	n/a	Low
34. Wittkampf et al. (2009)	✓	✓	✓	Low	✓	?	n/a	n/a	Unclear
35. Zhang et al. (2013)	✓	✓	?	Unclear	?	✓	?	?	Unclear
36. Zuithoff et al. (2010)	✓	✓	✓	Low	✓	✓	✓	?	Unclear

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Table 4: Quality assessment of included studies in the summed item scoring method cut-off point 10 meta-analysis (Moriarty et al., 2015) (continued)

Study	Reference test: Reference test	Reference test: Reference test	Reference test: If translated,	Reference test: If translated, psychometric	Reference test: Overall risk of	Flow / timing: Interval of two	Flow / timing: All participants	Flow / timing: All participants	Flow / timing: Overall risk of

	correctly classifies target condition	interpreted blind to PHQ-9	appropriate translation	properties reported	bias	weeks or less	receive same reference test	included in analysis?	bias
Allegiant studies									
13. Gräfe et al. (2004)	✓	?	n/a	n/a	Unclear	✓	✓	✓	Low
16. Kroenke et al. (2011)	✓	✓	n/a	n/a	Low	✓	✓	✓	Low
22. Navinés et al. (2012)	✓	✓	?	?	Unclear	✓	✓	✓	Low
29. Thekkumpurath et al. (2010)	✓	✓	n/a	n/a	Low	?	✓	✓	Unclear
33. Williams et al. (2005)	✓	?	n/a	n/a	Unclear	?	✓	✓	Unclear
Non-allegiant studies									
1. Adewuya et al. (2006)	✓	✓	n/a	n/a	Low	✓	✓	✓	Low
2. Arroll et al.	✓	✓	n/a	n/a	Low	?	✓	✓	Unclear

(2010)									
3. Azah et al. (2005)	✓	✓	✓	✓	Low	✓	✓	✗	High
4. Chagas et al. (2013)	✓	✓	?	?	Unclear	✓	✓	✗	High
6. de Lima Osorio et al. (2009)	✓	?	n/a	n/a	Unclear	?	✓	✓	Unclear
7. Elderon et al. (2011)	✓	✓	n/a	n/a	Low	✓	✓	✓	Low
8. Fann et al. (2005)	✓	?	n/a	n/a	Unclear	✓	✓	✗	High
9. Fine et al. (2013)	✓	?	n/a	n/a	Unclear	?	✓	✓	Unclear
10. Gelaye et al. (2013)	✓	✓	✓	✓	Low	✓	✓	✗	High
11. Gilbody et al. (2007)	✓	✓	n/a	n/a	Low	?	✓	✓	Unclear
12. Gjerdingen	✓	?	n/a	n/a	Unclear	✓	✓	✗	High

et al. (2009)									
14. Hyphantis et al. (2011)	✓	✓	?	?	Unclear	✓	✓	✗	High
15. Khamseh et al. (2011)	✓	✓	✓	?	Unclear	✓	✓	?	Unclear
19. Liu et al. (2011)	✓	✓	✓	✓	Low	✓	✓	?	Unclear
20. Lotrakul et al. (2008)	✓	✓	✓	✓	Low	?	✓	✗	High
23. Patel et al. (2008)	✓	✓	✓	?	Unclear	?	✓	✗	High
24. Phelan et al. (2010)	✓	✓	n/a	n/a	Low	✓	✓	✓	Low
25. Rooney et al. (2013)	✓	?	n/a	n/a	Unclear	?	✓	✗	High
26. Sherina et al. (2012)	✓	✓	✓	✓	Low	✓	✓	✓	Low
27. Sidebottom	✓	✓	n/a	n/a	Low	✓	✓	✗	High

et al. (2012)									
28. Stafford et al. (2007)	✓	✓	n/a	n/a	Low	✓	✓	✗	High
30. Thombs et al. (2008)	?	✓	n/a	n/a	Unclear	✓	✓	✓	Low
32. Watnick et al. (2005)	✓	✓	n/a	n/a	Low	✓	✓	✓	Low
34. Wittkampf et al. (2009)	✓	✓	n/a	n/a	Low	?	✓	✗	High
35. Zhang et al. (2013)	✓	?	✓	✓	Unclear	✗	✓	✗	High
36. Zuithoff et al. (2010)	✓	✓	?	?	Unclear	?	✓	✓	Unclear

Table 5. Pooled estimates of diagnostic properties of the PHQ-9 at cut-off point 10 and using algorithm scoring method in the non-independent vs independent studies groups

Settings	No of studies	No of patients	Sensitivity (95% CI)	Specificity (95% CI)	Pooled positive likelihood ratio (95% CI)	Pooled negative likelihood ratio (95% CI)	Diagnostic odds ratio (95% CI)	Heterogeneity: I^2

Manea et al, 2014 SR – RA group	7	4,065	0.77 (0.70 – 0.84)	0.94 (0.90 – 0.97)	14.97 (8.39 – 26.71)	0.23 (0.17 - 0.31)	64.40 (34.15 – 121.43)	78.9%
Manea et al, 2014 SR Independent studies	21	9,900	0.48 (0.41 – 0.91)	0.94 (0.91 – 0.95)	8.26 (6.15 – 11.09)	0.54 (0.48 – 0.62)	15.05 (11.03 – 20.52)	68.1%
Moriarty et al., 2015 SR – RA group	5	6,188	0.87 (0.77 – 0.93)	0.87 (0.76 – 0.94)	7.24 (3.74 – 14.03)	0.14 (0.08 - 0.25)	49.31 (25.74 – 94.48)	55.1%
Moriarty et al., 2015 SR Independent studies	26	13,164	0.76 (0.67 – 0.83)	0.88 (0.85 – 0.91)	6.72 (5.06 – 8.92)	0.26 (0.19 - 0.37)	24.96 (14.81 – 42.08)	81.5%

Figure legends

Figure 1. PHQ-9 algorithm scoring method summary ROC plot for the diagnosis of major depressive disorder in allegiant studies and non-allegiant studies. Pooled sensitivity and specificity estimates using a bi-variate meta-analysis (*HSROC* hierarchical receiver-operating characteristic).

Figure 2. PHQ-9 summed items scoring method at cut-off point 10 summary ROC plot for diagnosis of major depressive disorder in allegiant studies and non-allegiant studies. Pooled sensitivity and specificity estimates using a bi-variate meta-analysis (*HSROC* hierarchical receiver-operating characteristic).

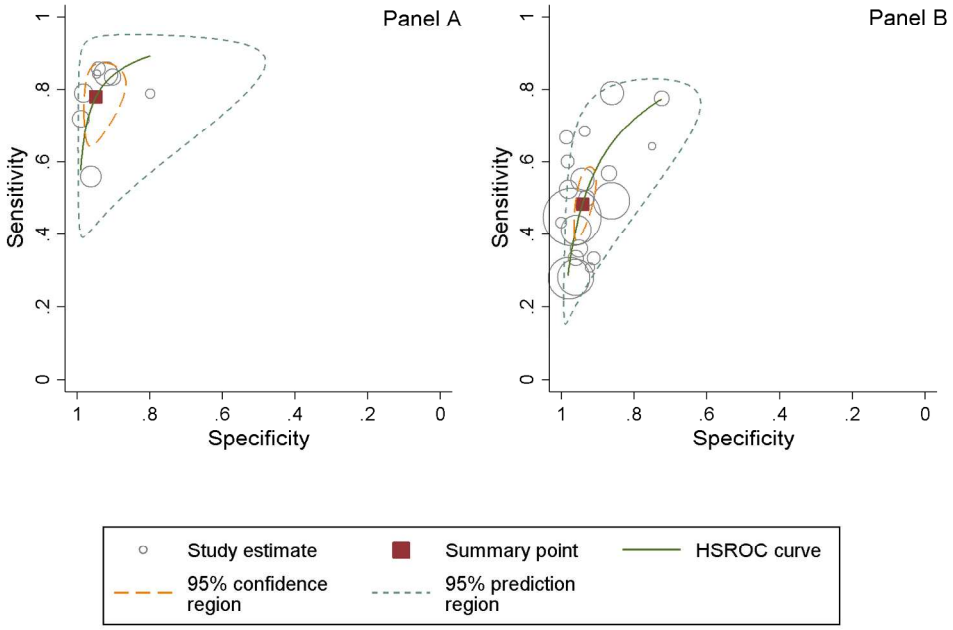
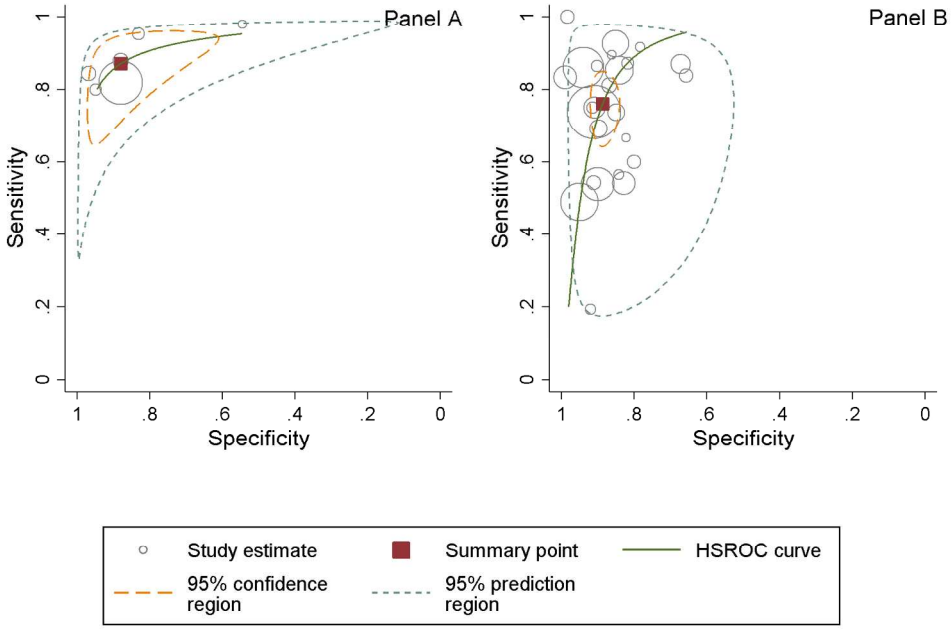


Figure 1. PHQ-9 algorithm scoring method summary ROC plot for the diagnosis of major depressive disorder in allegiant studies (Panel A) and non-allegiant studies (Panel B). Pooled sensitivity and specificity estimates using a bi-variate meta-analysis (HSROC hierarchical receiver-operating characteristic).

169x123mm (300 x 300 DPI)



Caption : Figure 2. PHQ-9 summed items scoring method at cut-off point 10 summary ROC plot for diagnosis of major depressive disorder in allegiant studies (panel A) and non-allegiant studies (panel B). Pooled sensitivity and specificity using a bi-variate meta-analysis (HSROC hierarchical receiver-operating characteristic).

169x123mm (300 x 300 DPI)

Appendices to: Manea L, Boehnke JR, Gilbody S, Moriarty AS, McMillan D, Are there researcher allegiance effects in diagnostic validation studies of the PHQ-9? A systematic review and meta-analysis. Manuscript submitted for publication at BMJOpen.

Appendix 1: Search terms used in Embase, MEDLINE and PsycINFO

(phq adj5 “9”).ti,ab.

(phq adj5 item$).ti,ab.

(patient health questionnaire adj5 “9”).ti,ab.

(patient health questionnaire adj5 item$).ti,ab.

(prime md adj5 “9”).ti,ab.

(prime md adj5 item$).ti,ab.

Appendix 2

Figure 1: PRISMA flowchart - search and selection of included diagnostic accuracy studies for the systematic review of studies reporting diagnostic accuracy of the PHQ-9 at using the summed items scoring method (Manea et al, 2014)

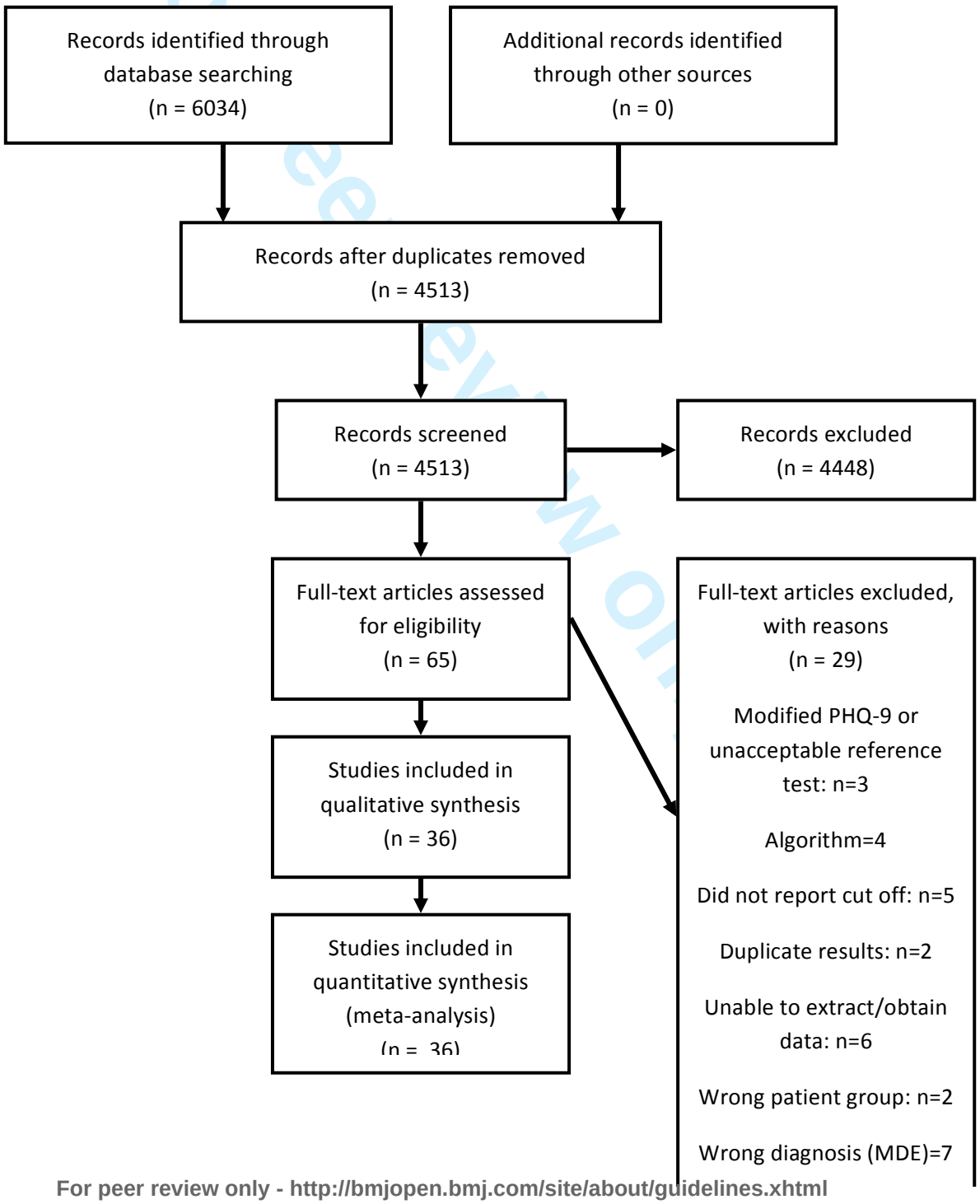
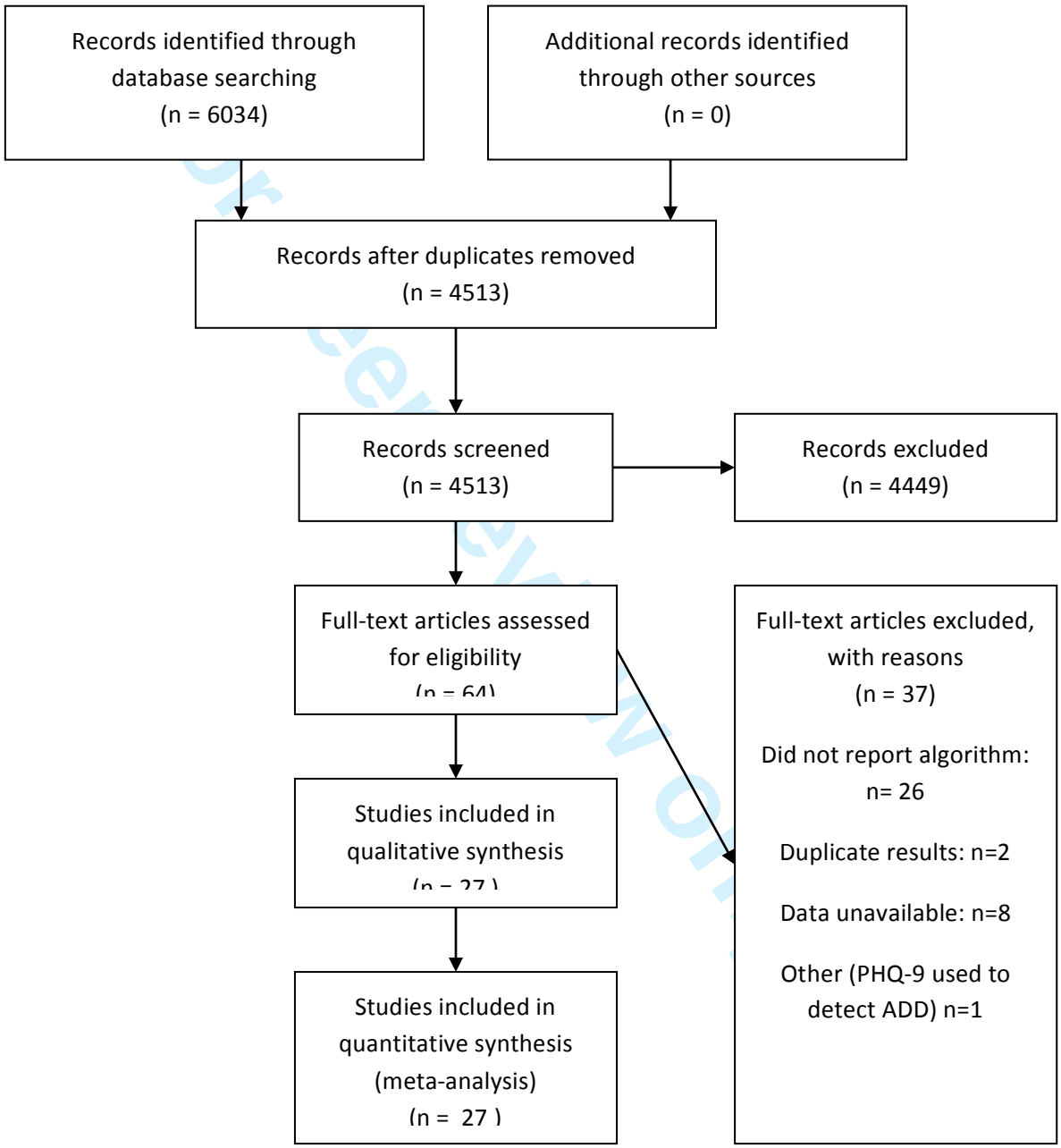


Figure 2: PRISMA flowchart - search and selection of included diagnostic accuracy studies for the systematic review of studies reporting diagnostic accuracy of the PHQ-9 at using the algorithm scoring method (Moriarty et al., 2015)



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
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).	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.	No
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
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
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Available online (see Manea et al., 2015; Moriarty et al., 2015)
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
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.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5-6
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

PRISMA 2009 Checklist

Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
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

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).	6, 21
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	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.	Tables 1 and 2
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).	Tables 3 and 4
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.	N/A
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Table 5
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Tables 3 and 4
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	11 and 17
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).	17-21
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).	21
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	21-22
FUNDING			

PRISMA 2009 Checklist

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.	23

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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