External Validation of a Shortened Screening Tool Using Individual Participant Data Meta-Analysis: a Case Study of the Patient Health Questionnaire-Dep-4

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Abstract

Shortened versions of self-reported questionnaires may be used to reduce respondent burden. When shortened screening tools are used, it is desirable to maintain equivalent diagnostic accuracy to full-length forms. This manuscript presents a case study that illustrates how external data and individual participant data meta-analysis can be used to assess the equivalence in diagnostic accuracy between a shortened and full-length form. This case study compares the Patient Health Questionnaire-9 (PHQ-9) and a 4-item shortened version (PHQ-Dep-4) that was previously developed using optimal test assembly methods. Using a large database of 75 primary studies (34,698 participants, 3,392 major depression cases), we evaluated whether the PHQ-Dep-4 cutoff of ≥ 4 maintained equivalent diagnostic accuracy to a PHQ-9 cutoff of ≥ 10. Using this external validation dataset, a PHQ-Dep-4 cutoff of ≥ 4 maximized the sum of sensitivity and specificity, with a sensitivity of 0.88 (95% CI 0.81, 0.93), 0.68 (95% CI 0.56, 0.78), and 0.80 (95% CI 0.73, 0.85) for the semi-structured, fully structured, and MINI reference standard categories, respectively, and a specificity of 0.79 (95% CI 0.74, 0.83), 0.85 (95% CI 0.78, 0.90), and 0.83 (95% CI 0.80, 0.86) for the semi-structured, fully structured, and MINI reference standard categories, respectively. While equivalence with a PHQ-9 cutoff of ≥ 10 was not established, we found the sensitivity of the PHQ-Dep-4 to be non-inferior to that of the PHQ-9, and the specificity of the PHQ-Dep-4 to be marginally smaller than the PHQ-9.

Keywords: Optimal Test Assembly; Sensitivity; Specificity; Equivalence Testing; Self-report questionnaire

Highlights

1) Optimal Test Assembly is a reproducible and replicable method to create shorter forms and reduce burden on respondents
2) This manuscript is the first paper to externally validate a measure developed through optimal test assembly methods
3) In our validation of the Patient Health Questionnaire 4-item shortened form, we found that the same cutoff maximized diagnostic accuracy
4) We found that sensitivity was non-inferior to that of the full-length form, but the specificity was slightly reduced.

INTRODUCTION

Self-reported symptom measures are used to assess mental health symptoms and may also be used to screen for mental disorders. However, in clinical practice and research, individuals may be asked to complete several measures, each with multiple items or domains, which can be demanding on their time, and sensitive items, such as asking about suicidal ideation, may be emotionally burdensome [1]–[4]. Long measures can result in poor data quality and high amounts of missing data. Thus, shortened forms that do not significantly reduce diagnostic accuracy can provide meaningful data while reducing respondent burden and potentially increasing data quality.

The Patient Health Questionnaire-9 (PHQ-9) is a 9-item, self-report questionnaire that measures depressive symptoms [5]–[7]. Scores on each item on the PHQ-9 range reflect symptoms in the last 2 weeks and range from 0 (“not at all”) to 3 (“every day”). Scores range from 0 to 27 with higher scores indicating higher levels of depressive symptomatology.

An individual participant data meta-analysis (IPDMA) on the accuracy of the PHQ-9 to screen for major depression was conducted on 29 studies with a semi-structured diagnostic interview as the reference standard (6,725 participants, 924 major depression cases). This study found that the standard and most commonly used for the PHQ-9, cutoff threshold of ≥ 10, maximized the combination of sensitivity (0.88, 95% CI 0.83, 0.92) and specificity (0.85, 95% CI 0.82, 0.88) [8].

Using a subset of data from the IPDMA, a previous study developed a 4-item shortened form of the PHQ-9, known as the PHQ-Dep-4, through optimal test assembly (OTA) methods. As with the PHQ-9, scores on each item of the PHQ-Dep-4 reflect symptoms in the last 2 weeks

and range from 0 (“not at all”) to 3 (“every day”). PHQ-Dep-4 scores range from 0 to 12 with higher scores indicating higher levels of depressive symptomatology.

The initial development study used 20 primary studies (7,850 participants, 863 major depression cases), which we refer to as the development sample, that administered the English version of the PHQ-9 and used a validated semi-structured or fully structured diagnostic interview (Mini International Neuropsychiatric Interview [MINI] excluded) to classify major depression. The PHQ-Dep-4 includes items 1, 2, 6, and 8 from the PHQ-9, representing depressed mood, loss of interest/pleasure, low self-esteem/guilt and psychomotor agitation [9]. OTA is a mixed-integer programming procedure that uses an estimated item response theory model to select the subset of items that best satisfies pre-specified constraints. In the case of the PHQ-Dep-4 development study, there were pre-specified constraints on the concurrent validity, reliability, and equivalency of diagnostic accuracy of the shortened form with the full-length form [10]. Although more commonly used in the development of high-stakes educational tests [11], recent studies have demonstrated that OTA can be used to develop shortened versions of patient-reported outcome measures [9], [12]–[17]. This procedure was shown in a simulation study to be replicable and reproducible, and produce shortened forms of minimal length with limited loss of information [14].

A cutoff of ≥ 4 on the PHQ-Dep-4 was found to perform equivalently to the PHQ-9 cutoff ≥ 10 in the development sample. However, accuracy of the PHQ-Dep-4 has not been externally validated outside of the development sample. It is therefore necessary to investigate whether a cutoff of ≥ 4 on the PHQ-Dep-4 continues to maintain equivalent diagnostic accuracy to the PHQ-9 cutoff ≥ 10. Conducting an external validation of this cutoff allows for the assessment of whether this cutoff was specific to the development dataset or generalizable to

other studies or applications in the future. In particular, the development of the PHQ-Dep-4 was based on comparing properties of the full-length form to a set of candidate shortened forms in the development sample, and thus is susceptible to issues of overfitting or a lack of generalizability. By conducting an external validation, it is possible to see whether the equivalence in accuracy of the PHQ-Dep-4 to the PHQ-9 can be confirmed in an independent dataset.

The objective of the present study was to use data from a unique set of studies that administered the PHQ-9 as well as a validated semi-structured or fully structured diagnostic interview for major depression to validate the diagnostic accuracy of the previously developed PHQ-Dep-4. Specifically, we (1) estimated accuracy for all possible PHQ-Dep-4 cutoffs (i.e., ≥ 1 to ≥ 12), and (2) tested equivalency in accuracy for each PHQ-Dep-4 cutoff to that of a PHQ-9 cutoff of ≥ 10, with the comparison of the PHQ-Dep-4 cutoff of ≥ 4 considered the primary comparison.

METHODS

The present validation study used data synthesized from an updated IPDMA of the screening accuracy of the PHQ-9 for major depression [8], [18], excluding datasets that were included in the original PHQ-Dep-4 development project [9]. The present validation study included studies conducted in any language and using any validated semi-structured or fully structured diagnostic interview (MINI included). The main IPDMA was registered in PROSPERO (CRD42014010673) and a protocol was published [19]. The present analysis was not part of the protocol for the main IPDMA, but a separate protocol was developed and posted prior to initiation at https://osf.io/xy2b8/.

The Main IPDMA Database

Study selection

In the main IPDMA, datasets from articles in any language were eligible for inclusion if (1) they included PHQ-9 scores; (2) they included diagnostic classifications for current Major Depressive Episode (MDE) or Major Depressive Disorder (MDD) based on Diagnostic and Statistical Manual of Mental Disorders (DSM) [20]–[23], or International Classification of Diseases (ICD) [24] criteria, using a validated semi-structured or fully structured interview; (3) the PHQ-9 and diagnostic interview were administered within two weeks of each other, since diagnostic criteria for major depression are for symptoms in the last two weeks; (4) participants were ≥ 18 years and not recruited from youth or school-based settings; and (5) participants were not recruited from psychiatric settings or because they were identified as having symptoms of depression, since screening is done to identify unrecognized cases. Datasets where not all participants were eligible were included if primary data allowed selection of eligible participants.

Database sources and search strategy

A medical librarian searched Medline, Medline In-Process & Other Non-Indexed Citations via Ovid; PsycINFO; and Web of Science from January 1, 2000 to May 9, 2018 using a peer-reviewed search strategy (eMethods1) [25]. The search was limited to the year 2000 onwards because the PHQ-9 was first published in 2001 [7]. We also reviewed reference lists of relevant reviews and queried contributing authors about non-published studies. Search results were uploaded into RefWorks (RefWorks-COS, Bethesda, MD, USA). After deduplication, remaining citations were uploaded into DistillerSR (Evidence Partners, Ottawa, Canada) for processing review results.

Two investigators independently reviewed titles and abstracts for eligibility. If either investigator deemed a study potentially eligible, full-text review was done by two investigators, independently, with disagreements resolved by consensus, consulting a third investigator when

necessary. Translators were consulted for languages other than those for which team members were fluent.

Data contribution and synthesis

Authors of eligible datasets were invited to contribute de-identified primary data, including PHQ-9 scores and major depression status. We emailed corresponding authors of eligible primary studies at least three times, as necessary, with at least two weeks between each email. If we did not receive a response, we emailed co-authors and attempted to contact corresponding authors by phone.

Individual participant data were converted to a standard format and synthesized into a single dataset with study-level data. We compared published participant characteristics and diagnostic accuracy results with results from raw datasets and resolved any discrepancies in consultation with the original investigators.

To define major depression, we considered MDD or MDE based on the DSM or ICD. If more than one was reported, we prioritized MDE over MDD, since screening would attempt to detect depressive episodes and further interview would determine if the episode were related to MDD, bipolar disorder, or persistent depressive disorder. When both were present, we prioritized DSM over ICD, because DSM is more commonly used in existing studies.

Data Used in the Present Analyses

To consider an independent data source for this validation, we excluded the 20 studies that were included in the original PHQ-Dep-4 development project. We note that these 20 studies were originally used in the development paper because of their availability at the time that study was conducted, rather than a deliberate splitting of the sample. In addition, to be able to calculate PHQ-Dep-4 scores, we excluded studies and participants without item-level PHQ-9 data.

Statistical Analyses

Using the item-level PHQ-9 data, we calculated PHQ-Dep-4 scores by summing the item scores from PHQ-9 items 1 (loss of interest), 2 (depressed mood), 6 (feeling like a failure), and 8 (physical movement). We then conducted two sets of analyses.

To assess diagnostic accuracy, we estimated sensitivity and specificity. Sensitivity, the true positive rate, refers to the probability of scoring above the cutoff in question given that the participant was classified with MDE or MDD based on DSM or ICD criteria using a validated semi-structured or fully structured interview. Specificity, the true negative rate, refers to the probability of scoring below the cutoff in question given that the participant was classified with MDE or MDD based on DSM or ICD criteria using a validated semi-structured or fully structured interview.

First, we estimated sensitivity and specificity for all possible PHQ-Dep-4 cutoffs (i.e., ≥ 1 to ≥ 12), as well as the standard PHQ-9 cutoff score of ≥ 10, which maximizes sensitivity + specificity [8], [18]. For each PHQ-Dep-4 cutoff, separately, and for a PHQ-9 cutoff of ≥ 10, we fit bivariate random-effects models using adaptive Gauss-Hermite quadrature with one quadrature point [26]. This is a 2-stage meta-analytic approach that synthesizes sensitivity and specificity simultaneously and accounts for the correlation between them, as well as for precision of estimates within studies. For each analysis, this model provided estimates of pooled sensitivity and specificity.

The formulation of the model can be expressed as the following. Let $y_{s,i}^{(0)}$ be the dichotomous outcome of the screening test (PHQ-9 or PHQ-Dep-4) for the *i*-th participant in the *s*-th primary study who does not have a true depression diagnosis. Therefore, $y_{s,i}^{(0)}$ is equal to one when the participant has a high score on the screening test and zero when the participant has a low score on the screening test. Similarly, let $y_{s,i}^{(1)}$ be the dichotomous outcome of the screening

test for the *i*-th participant of the *s*-th primary study who does have a true depression diagnosis. The model is formulated as:

$$y_{s,i}^{(0)} \sim Bernoulli(p_{s,i}^{(0)})$$

$$logit\left(p_{s,i}^{(0)}\right) = \mu_s^{(0)} = \mu^{(0)} + u_s^{(0)}$$

$$y_{s,i}^{(1)} \sim Bernoulli(p_{s,i}^{(1)})$$

$$logit\left(p_{s,i}^{(1)}\right) = \mu_s^{(1)} = \mu^{(1)} + u_s^{(1)}$$

$$\boldsymbol{u}_s = \begin{pmatrix} u_s^{(0)} \\ u_s^{(1)} \end{pmatrix} \sim N(0, \boldsymbol{\Sigma})$$

$$\boldsymbol{\Sigma} = \begin{pmatrix} \tau_0^2 & \tau_0\tau_1\rho_\tau \\ \tau_0\tau_1\rho_\tau & \tau_1^2 \end{pmatrix}$$

In this case, the false positive rate (FPR), which is equal to 1 – specificity, and the true positive rate (TPR), which is the sensitivity, can be estimated for the pooled logit(FPR) and logit(TPR) through $\hat{\mu}^{(0)}$and $\hat{\mu}^{(1)}$, respectively. $\hat{\tau}^{(0)}$and $\hat{\tau}^{(1)}$estimates the between-study variance of the logit-transformed parameters, and $\widehat{\rho_\tau}$ is the estimated correlation.

For these analyses, we modeled sensitivity and specificity separately among studies that used each reference standard category (semi-structured, fully structured, or MINI) as well as pooled together. We present accuracy results for the PHQ-Dep-4 separately by reference standard type because previous studies have found that there are important differences in the design and performance of different types of diagnostic interviews used as reference standards [27]–[30], and that PHQ-9 sensitivity and specificity vary across different reference standards [8], [18]. For each reference standard category, we constructed an empirical receiver operating characteristic (ROC) plot for the PHQ-Dep-4 based on pooled sensitivity and specificity

estimates from each cutoff. Separately, we marked the point in ROC-space for a PHQ-9 cutoff of ≥ 10.

Second, we tested the equivalence of the PHQ-Dep-4 and PHQ-9. The comparison of the PHQ-Dep-4 cutoff of ≥ 4 to the PHQ-9 cutoff of ≥ 10 was considered as our primary analysis. For these analyses, we pooled reference standard categories together, because although PHQ-9 and PHQ-Dep-4 sensitivity and specificity may differ by reference standard category, we did not believe that *differences* in sensitivity and specificity between PHQ-Dep-4 cutoffs and a PHQ-9 cutoff of ≥ 10 would vary by reference standard category, since each primary study compared the PHQ-Dep-4 and PHQ-9 to the same reference standard. By pooling, we increase power and therefore reduce the risk of an ambiguous outcome in the analysis. In line with this, a previous comparison of the PHQ-8 and PHQ-9 found that although accuracy differed across reference standard categories, differences in accuracy across the forms were similar across reference standard categories [31]. We estimated the crude differences in sensitivity and specificity between each PHQ-Dep-4 cutoff and a PHQ-9 cutoff of ≥ 10 and constructed confidence intervals (CI) for differences via the cluster bootstrap approach [32], [33], resampling at study and subject levels with replacement. For each comparison, we ran 1000 iterations of the bootstrap. These CIs allowed us to test whether the sensitivity and specificity of each PHQ-Dep-4 cutoff are equivalent to that of the PHQ-9 based on a pre-specified minimally important difference of $\delta = 0.05$ [34], as has been done in previous studies [9], [13], [31]. That is, for each cutoff, for differences in sensitivity and specificity separately, we would consider the null hypothesis that there are differences large enough to be important and test that against the alternative hypothesis that there are no meaningful differences. If the entire CI is included within the interval of − 0.05 to + 0.05, we would reject the null hypothesis and conclude that

equivalence is present. If the entire CI is outside of the interval, we would conclude that the accuracies are not equivalent. If the CIs cross the interval of − 0.05 to + 0.05, findings would be deemed ambiguous, and the equivalence would be found to be indeterminate. Lastly, we determined which PHQ-Dep-4 cutoff showed the smallest overall sum of absolute differences in accuracy (i.e. in sensitivity and in specificity) compared to PHQ-9 ≥ 10.

All analyses were conducted in R (R version R 3.4.1 [35], RStudio version 1.0.143) using the *glmer* function within the *lme4* package [36]. All R code used to run the analysis is included in the supplementary materials, however due to data sharing agreements, the raw data is not available.

Ethics

As this study involves secondary analysis of de-identified previously collected data, the Research Ethics Committee of the Jewish General Hospital determined that it did not require research ethics approval. However, for each included dataset, we confirmed that the original study received ethics approval and that all participants provided informed consent.

RESULTS

Search Results and Dataset Inclusion

Figure 1 illustrates the study flow diagram. Of 9,670 unique titles and abstracts identified from database searches, 9,199 were excluded at the title and abstract review stage and 297 after full-text review. After removing duplicate samples, adding unpublished studies contributed by authors, excluding studies that did not have item level data or were included in the PHQ-Dep-4 development paper, there were 75 eligible datasets (N participants = 34,698; N major depression = 3,392 [prevalence 10%]) that contributed data for our analysis.

Of the 75 included studies, 29 (7,719 participants; 923 major depression cases) used a semi-structured interview as the reference standard, 15 (12,109 participants; 873 cases) used a fully structured interview (other than the MINI), and 31 (14,870 participants; 1,596 cases) used the MINI. The Structured Clinical Interview for the DSM (SCID) was the most commonly used semi-structured interview (28 of 29 studies) and the Composite International Diagnostic Interview (CIDI) the most commonly used fully structured interview (14 of 15 studies). See Supplementary Table 1a-c for characteristics of included primary studies, eligible excluded primary studies, and the 20 studies included in the PHQ-Dep-4 development paper only. Table 1 presents participant-level descriptive statistics for the sample used in the present study.

Validation Results

Figure 2 shows receiver-operating curves for each reference standard category as well as the PHQ-9 cutoff score of ≥ 10. Table 2 shows estimated sensitivity and specificity for PHQ-Dep-4 cutoffs (≥ 1 to ≥ 12), as well as the standard and optimal PHQ-9 cutoff score of ≥ 10. For a PHQ-Dep-4 cutoff of ≥ 4, sensitivity was 0.88 (95% CI 0.81, 0.93), 0.68 (95% CI 0.56, 0.78), and 0.80 (95% CI 0.73, 0.85) for the semi-structured, fully structured, and MINI reference standard categories, respectively, as compared to 0.88 (0.81, 0.93), 0.64 (0.50, 0.76), and 0.73 (0.66, 0.79) for the PHQ-9 cutoff of ≥ 10, respectively. Similarly, for a PHQ-Dep-4 cutoff of ≥ 4, specificity was 0.79 (95% CI 0.74, 0.83), 0.85 (95% CI 0.78, 0.90), and 0.83 (95% CI 0.80, 0.86) for the semi-structured, fully structured, and MINI reference standard categories, respectively, as compared to 0.85 (0.80, 0.88), 0.89 (0.83, 0.93), and 0.89 (0.86, 0.91) for the PHQ-9 cutoff of ≥ 10, respectively. Figure 2 shows the ROC plots for each reference standard category.

Table 3 shows the results of the tests of equivalence of the PHQ-Dep-4 and PHQ-9 pooled across all reference standard categories. A PHQ-Dep-4 cutoff of ≥ 4 showed the smallest

overall sum of absolute differences in accuracy with PHQ-9 ≥ 10, with a difference in sensitivity of 0.03 (95% CI 0.00, 0.06) and a difference in specificity of -0.05 (95% CI -0.07, -0.04). These findings were ambiguous, as the CIs for both sensitivity and specificity crossed the interval of -0.05 to +0.05. No other PHQ-Dep-4 cutoff indicated equivalency for both sensitivity and specificity. The next closest PHQ-Dep-4 cutoff to PHQ-9 ≥ 10 was a PHQ-Dep-4 cutoff of ≥ 5, with a difference in sensitivity of -0.07 (95% CI -0.11, -0.05) and a difference in specificity of 0.02 (95% CI 0.01, 0.03).

DISCUSSION

This study used data from 75 primary studies to assess whether a previously determined PHQ-Dep-4 cutoff of ≥ 4, which was equivalent to a PHQ-9 cutoff of ≥ 10 in a development sample, would also be equivalent in a validation sample. While a PHQ-Dep-4 cutoff of ≥ 4 showed the best performance among all possible PHQ-Dep-4 cutoffs compared to the PHQ-9 cutoff of ≥ 10, the equivalence results were ambiguous, and we were unable to conclude that its specificity was equivalent to that of the PHQ-9 cutoff of ≥ 10.

We found that compared to the standard and optimal PHQ-9 cutoff of ≥ 10, a PHQ-Dep- cutoff of ≥ 4 had slightly greater sensitivity and slightly reduced specificity. The next best PHQ-Dep-cutoff of ≥ 5 had slightly greater specificity and slightly reduced sensitivity. In clinical settings, use of shortened forms such as the PHQ-Dep-4 offers the advantage of reducing respondent burden. While our study assessed the sum of sensitivity and specificity, this does not necessarily reflect local concerns such as the capacity for conducting further assessments, nor does it necessarily maximize the likelihood of patient benefits or minimize costs and harms. We note that clinicians and researchers can choose different cut-offs based on local priorities and resources using the information provided in Tables 2 and 3.

While a strength of this analysis is the large number of primary studies included in the dataset, these primary studies spanned a large number of languages. This can cause concern for differential item functioning (DIF). The items for the PHQ-Dep-4 were not selected with regards to considerations of DIF. However, studies of DIF with the PHQ-9 have shown that it performs equivalently or with minimal impact of DIF across multiple languages [37]–[39]. We note that future research may wish to specifically investigate the impact of DIF for the PHQ-Dep-4 in comparison to the PHQ-9.

The development study tested non-inferiority rather than equivalency. The development study found a difference in sensitivity of +0.03, and a difference in specificity of -0.03 between the two forms [9]. The present study found differences of +0.03 and -0.05, respectively. While equivalency is therefore not established, the findings in the present study were not substantively different from the development study.

While it is not clear that the PHQ-Dep-4 performs equivalently to the PHQ-9 for specificity, clinicians screening for depression may opt to use the PHQ-Dep-4 with the understanding that depending on the cutoff used, specificity might be slightly reduced compared to the full PHQ-9 at cutoff of ≥ 10. Furthermore, clinicians should be aware that while the full PHQ-9 aligns with the nine DSM symptoms for major depression, not all PHQ-9 items may be relevant to individual presentations of a given mental disorder, and the PHQ-Dep-4 includes only a pre-specified subset of four items (1, 2, 6, and 8), thus not necessarily capturing the specific symptoms of a given patient.

There are several reasons that may explain why equivalence could not be concluded. First, although the overall sample size and number of studies used in this analysis was large, it could be that the study was underpowered, due to the design effect associated with the clustering

within studies. As we do not know of methods for calculating power to establish equivalency in accuracy based on sensitivity and specificity difference for a subset of items compared to the total set, it was not possible to determine the necessary sample size needed *a priori*. Furthermore, we also did not split the data by reference standard category and conduct separate analyses. Second, we found that sensitivity in the shortened form was improved as compared to the full-length form. However, the specificity of the shortened form was lower than that of the full-length form, resulting in the inability to conclude equivalence between the two forms.

There are several other possible limitations of this study. First, for the collection of data for the full IPDMA, we were unable to obtain data from 27 eligible studies. Of the studies that provided data, five were excluded because they did not include item-level scores necessary to calculate PHQ-Dep-4, and we excluded another 20 studies from the development dataset to provide us with a set of external validation data. With the final available dataset, we were unable to investigate equivalence in specific patient populations as that would have required splitting the data even further. Second, for our first set of analyses (estimating PHQ-Dep-4 accuracy at all cutoffs), primary studies were categorized based on the diagnostic interview used, but interviewers may not have always administered the interviews as intended, which could have influenced results. This study only compared the PHQ-Dep-4 to a PHQ-9 cutoff of ≥ 10 because, although some primary studies have found other preferred cutoffs, large IPDMAs have concluded that cutoff ≥ 10 maximizes the sum of sensitivity and specificity [8], [18]. Lastly, this study evaluated the items included in the PHQ-Dep-4 as previously developed and did not re-develop the shortened form. It could be that a different set of items, creating either a different form of length 4 or a potentially shorter or longer form, would result in equivalent sensitivity and specificity to the full PHQ-9.

CONCLUSION

In conclusion, this was the first study to our knowledge to externally validate the results of shortening a self-report questionnaire through the OTA method using individual participant level data. We found that the previously suggested cutoff of ≥ 4 for the PHQ-Dep-4 remained the preferred cutoff, but the specificity of the shortened form did not meet equivalency to the full PHQ-9 cutoff of ≥ 10. Clinicians may consider screening with the PHQ-Dep-4 to reduce respondent burden, but should be aware that in doing so, specificity may be slightly compromised compared to the full PHQ-9.

Contributions:

DH, BLevis, JPAI, PC, SBP, RCZ, ABenedetti, and BDT were responsible for the study conception and design. SM contributed as a patient partner knowledge user. FF contributed an included dataset. BLevis, YS, and BDT contributed to data extraction, coding, evaluation of included studies, and data synthesis. DH, BLevis, FF, ABenedetti, and BDT contributed to data analysis and interpretation. DH, BLevis, YS, ABenedetti, and BDT drafted the manuscript.

Members of the DEPRESSD PHQ Group contributed:

To data extraction, coding, and synthesis: CH, YW, AK, PMB, ZN, MImran, DBR, KER, MA, AWL. Via the design and conduct of database searches: JTB, LAK. As members of the DEPRESSD Steering Committee, including conception and oversight of collaboration: SG, DM. By contributing included datasets: DA, LA, HRB, ABeraldi, CNB, ABhana, RIB, MHC, JCNC, LFC, DC, AC, FMD, JMdMvG, CDQ, SF, JRWF, DF, ECG, BG, LG, LJG, EPG, BJH, LHantsoo, EEH, MHärter, UH, LHides, SEH, SH, MHudson, TH, MInagaki, HJJ, NJ, MEK, SK, BAK, YK, FL, MAL, HFLA, SIL, ML, SRL, BLöwe, NPL, CL, RAM, BPM, SMS, TNM, KM, JEMN, LN, FLO, PP, AP, SLP, TJQ, ER, SDR, KR, HJR, ISS, MTS, JS, EHS, LSpangenberg, LStafford, SCS, KS, PLLT, MTR, TDT, CMvdFC, TvH, HCvW, LIW, JLW, DW, KW, MY, QZZ, YZ.

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FIGURES

Figure 1: Flow diagram of study selection process

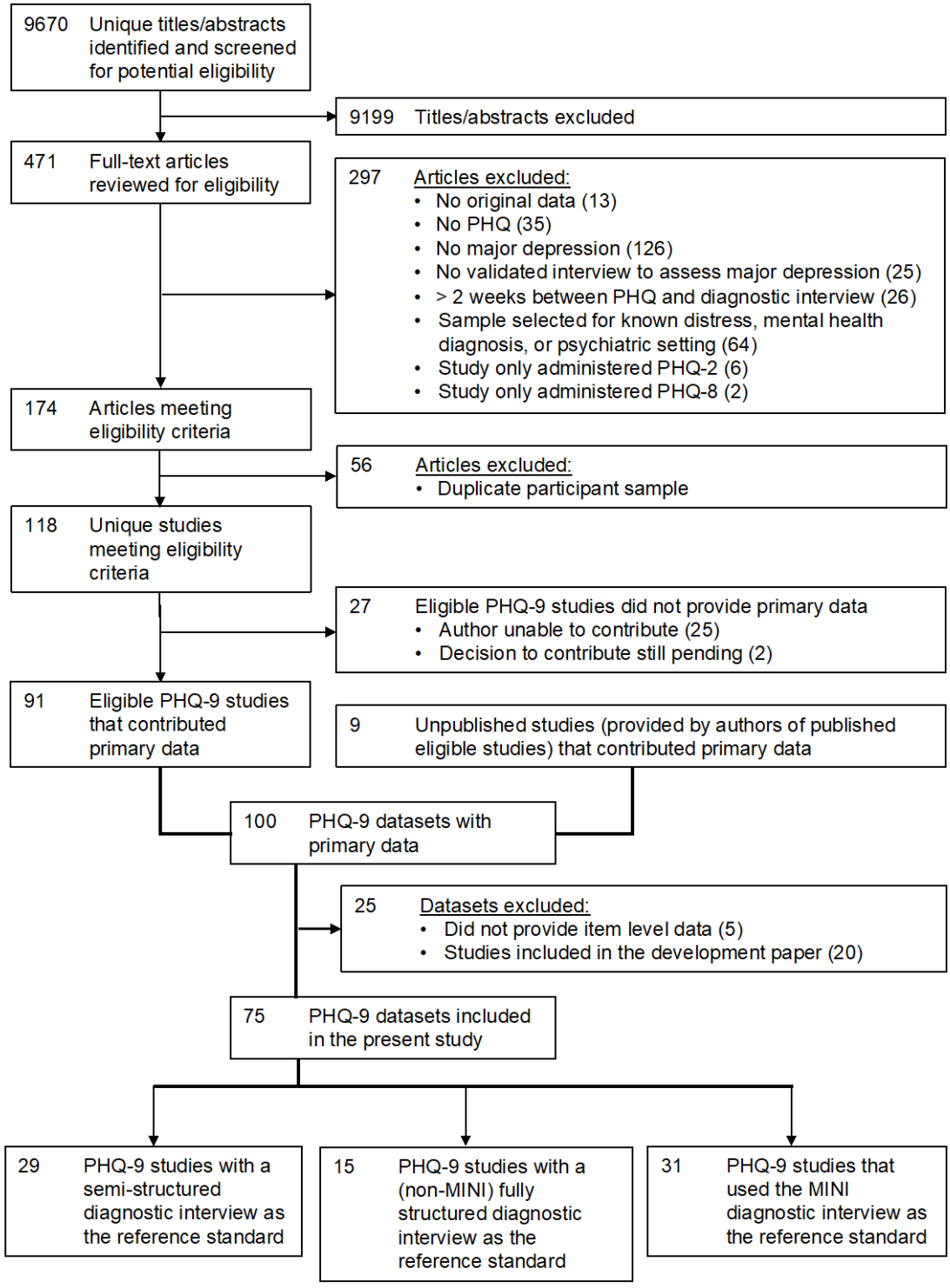
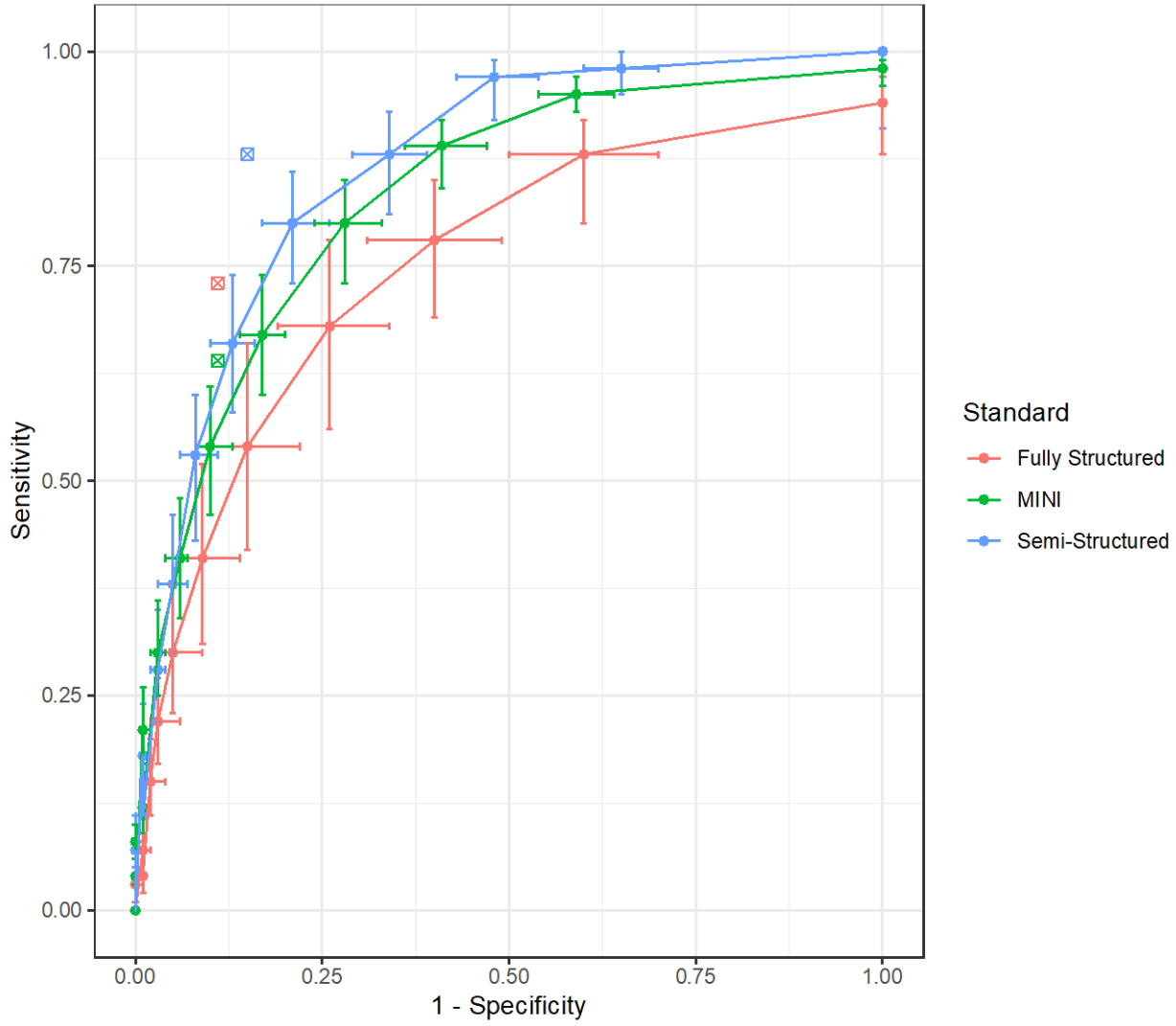


Figure 2: Receiver-operating curve for each reference standard category. Points represent cutoffs of 0 (right) to 12 (left) for each reference standard category. X marks the PHQ-9 cutoff of ≥ 10.



TABLES

Table 1: Demographics of the study sample for patients with and without major depression

Sociodemographic variables	Total (N=34,698)	Participants with Major Depression (N=3,392)	Participants without Major Depression (N=31,306)
Age in years, *mean [median] ± SD (range)*[1]	47.7 [48] ± 16.3 (18, 98)	46.4 [45] ± 16.3 (18, 94)	48.9 [48] ± 16.3 (18, 98)
Women, *n (%)*[2]	20678	2351 (11.4)	18327 (88.6)
Men, *n (%)*[2]	13998	1038 (7.4)	12960 (92.6)
PHQ-9 score, *mean [median] ± SD (range)*	4.9 [3] ± 5.2 (0, 27)	13.1 [13] ± 6.3 (0, 27)	4.0 [3] ± 4.2 (0, 27)
Country, *n (%)*			
Netherlands	7049	494 (7.0)	6555 (93.0)
Canada	5215	190 (3.6)	5025 (96.4)
South Korea	3071	205 (6.7)	2866 (93.3)
South Africa	2300	299 (13.0)	2001 (87.0)
China	2096	136 (6.5)	1960 (93.5)
Germany	1605	147 (9.2)	1458 (90.8)
Taiwan	1532	50 (3.3)	1482 (96.7)
Latvia	1467	147 (10.0)	1320 (90.0)
USA	1247	166 (13.3)	1081 (86.7)
Greece	1036	262 (25.3)	774 (74.7)
Spain	1003	83 (8.3)	920 (91.7)
Other[3]	7077	1213 (17.1)	5864 (82.9)
Language, *n (%)*[4]			
English	8073	562 (7.0)	7511 (93.0)
Dutch	7222	522 (7.2)	6700 (92.8)
Chinese	3597	164 (4.6)	3433 (95.4)
Korean	3071	205 (6.7)	2866 (93.3)
South African languages	1838	211 (11.5)	1627 (88.5)
German	1605	147 (9.2)	1458 (90.8)
Spanish	1540	181 (11.8)	1359 (88.2)
Greek	1036	262 (25.3)	774 (74.7)
Other[5]	6611	1130 (17.1)	5481 (82.9)
General Care Setting, *n (%)*			
Outpatient care	17624	2250 (12.8)	15374 (87.2)
Inpatient care	2781	331 (11.9)	2450 (88.1)
Non-medical setting	14163	806 (5.7)	13357 (94.3)
Outpatient/inpatient mixed sample	130	5 (3.8)	125 (96.2)
Diagnostic Interview, *n (%)*			
SCID	6187	873 (14.1)	5314 (85.9)
CIDI	11810	860 (7.3)	10950 (92.7)
SCAN	1532	50 (3.3)	1482 (96.7)
MINI	14870	1596 (10.7)	13274 (89.3)
CIS-R	299	13 (4.3)	286 (95.7)
Classification system, *n (%)*			
ICD-10	909	86 (9.5)	823 (90.5)

DSM-III	1107	104 (9.4)	1003 (90.6)
DSM-IV	31771	3089 (9.7)	28682 (90.3)
DSM-V	911	113 (12.4)	798 (87.6)

[1]N missing = 31 participants with major depression, 216 participants without major depression
[2]N missing = 3 participants with major depression, 19 participants without major depression
[3]Other countries: Ethiopia, Japan, Australia, Brazil, Singapore, Malaysia, India, Israel, Mexico, Thailand, Zimbabwe, Argentina, Uganda, Iran, Kenya, Belgium, Italy, UK, Myanmar, Nepal, Hong Kong China.
[4]N missing = 8 for MDD, 97 for non-MDD
[5]Other Languages: Amharic, Latvian, Japanese, Russian, Portuguese, Malay, Indian languages (unspecified), Malay or English, Thai, Shona, Hebrew, Farsi, Kiswahili, Italian, Burmese, Nepali, Malay, Chinese or Tamil, Filipino, Arabic, French

Table 2: Sensitivity and specificity for each PHQ-Dep-4 cutoff and the PHQ-9 cutoff of ≥ 10

	SEMI-STRUCTURED REFERENCE STANDARD: N studies = 29, N participants = 7719, N major depression = 923				**FULLY STRUCTURED REFERENCE STANDARD: N studies = 15, N participants = 12,109, N major depression = 873**				**MINI[2] REFERENCE STANDARD: N studies = 31, N participants = 14,870, N major depression = 1596**			
Cutoff PHQ-Dep-4	**sensitivity**	**95% CI**	**specificity**	**95% CI**	**sensitivity**	**95% CI**	**specificity**	**95% CI**	**sensitivity**	**95% CI**	**specificity**	**95% CI**
>= 1	1.00	(0.91, 1.00)	0.35	(0.30, 0.40)	0.94	(0.88, 0.97)	0.40	(0.30, 0.50)	0.98	(0.96, 0.99)	0.41	(0.36, 0.46)
>= 2	0.98	(0.95, 1.00)	0.52	(0.46, 0.57)	0.88	(0.80, 0.92)	0.60	(0.51, 0.69)	0.95	(0.93, 0.97)	0.59	(0.53, 0.64)
>= 3	0.97	(0.92, 0.99)	0.66	(0.61, 0.71)	0.78	(0.69, 0.85)	0.74	(0.66, 0.81)	0.89	(0.84, 0.92)	0.72	(0.67, 0.76)
>= 4	0.88	(0.81, 0.93)	0.79	(0.74, 0.83)	0.68	(0.56, 0.78)	0.85	(0.78, 0.90)	0.80	(0.73, 0.85)	0.83	(0.80, 0.86)
>= 5	0.80	(0.73, 0.86)	0.87	(0.84, 0.90)	0.54	(0.42, 0.66)	0.91	(0.86, 0.94)	0.67	(0.60, 0.74)	0.90	(0.87, 0.92)
>= 6	0.66	(0.58, 0.74)	0.92	(0.89, 0.94)	0.41	(0.31, 0.52)	0.95	(0.91, 0.97)	0.54	(0.46, 0.61)	0.94	(0.93, 0.96)
>= 7	0.52	(0.43, 0.60)	0.95	(0.93, 0.97)	0.30	(0.23, 0.38)	0.97	(0.94, 0.98)	0.41	(0.34, 0.48)	0.97	(0.96, 0.98)
>= 8[1]	0.38	(0.30, 0.46)	0.97	(0.96, 0.98)	0.22	(0.17, 0.27)	0.98	(0.96, 0.99)	0.30	(0.25, 0.36)	0.99	(0.98, 0.99)
>= 9	0.28	(0.22, 0.35)	0.99	(0.98, 0.99)	0.15	(0.11, 0.20)	0.99	(0.98, 0.99)	0.21	(0.17, 0.26)	0.99	(0.99, 0.99)
>= 10	0.18	(0.13, 0.24)	0.99	(0.99, 1.00)	0.07	(0.04, 0.12)	0.99	(0.99, 1.00)	0.12	(0.09, 0.16)	1.00	(0.99, 1.00)
>= 11	0.11	(0.08, 0.16)	1.00	(0.99, 1.00)	0.04	(0.02, 0.07)	1.00	(0.99, 1.00)	0.08	(0.06, 0.10)	1.00	(1.00, 1.00)
>= 12	0.07	(0.05, 0.11)	1.00	(1.00, 1.00)	0.03	(0.01, 0.06)	1.00	(1.00, 1.00)	0.04	(0.03, 0.06)	1.00	(1.00, 1.00)
PHQ-9 >= 10	0.88	(0.81, 0.93)	0.85	(0.80, 0.88)	0.64	(0.50, 0.76)	0.89	(0.83, 0.93)	0.73	(0.66, 0.79)	0.89	(0.86, 0.91)

[1]BOBYQA optimizer was used to ensure model convergence for the semi-structured reference category, as the model with the default optimizer did not converge

[2]MINI: Mini International Neuropsychiatric Interview

Table 3: Results of the equivalence tests between the accuracy of the PHQ-Dep-4 and PHQ-9 ≥ 10

All studies (N studies = 75, N participants = 34,698, N major depression = 3392)				
Cutoff	**Sensitivity Difference** (PHQ-Dep-4 - PHQ-9 >=10)	**95% CI**	**Specificity Difference** (PHQ-Dep-4 - PHQ-9 >=10)	**95% CI**
PHQ-Dep-4 >= 1	0.21	(0.14, 0.25)	-0.49	(-0.52, -0.46)
PHQ-Dep-4 >= 2	0.18	(0.13, 0.22)	-0.31	(-0.34, -0.28)
PHQ-Dep-4 >= 3	0.13	(0.09, 0.16)	-0.17	(-0.19, -0.15)
PHQ-Dep-4 >= 4	0.03	(0.00, 0.06)	-0.05	(-0.07, -0.04)
PHQ-Dep-4 >= 5	-0.07	(-0.11, -0.05)	0.02	(0.01, 0.03)
PHQ-Dep-4 >= 6	-0.22	(-0.27, -0.19)	0.06	(0.05, 0.08)
PHQ-Dep-4 >= 7	-0.35	(-0.41, -0.33)	0.09	(0.08, 0.11)
PHQ-Dep-4 >= 8	-0.47	(-0.53, -0.45)	0.11	(0.09, 0.13)
PHQ-Dep-4 >= 9	-0.55	(-0.62, -0.53)	0.12	(0.10, 0.14)
PHQ-Dep-4 >= 10	-0.65	(-0.72, -0.62)	0.12	(0.10, 0.15)
PHQ-Dep-4 >= 11	-0.70	(-0.77, -0.67)	0.13	(0.10, 0.15)
PHQ-Dep-4 >= 12	-0.73	(-0.80, -0.69)	0.13	(0.10, 0.15)

SUPPLEMENTARY MATERIALS

eMethods1: Search strategies

MEDLINE (OvidSP)

1. PHQ*.af.
2. patient health questionnaire*.af.
3. 1 or 2
4. Mass Screening/
5. Psychiatric Status Rating Scales/
6. "Predictive Value of Tests"/
7. "Reproducibility of Results"/
8. exp "Sensitivity and Specificity"/
9. Psychometrics/
10. Prevalence/
11. Reference Values/
12. Reference Standards/
13. exp Diagnostic Errors/
14. Mental Disorders/di, pc [Diagnosis, Prevention & Control]
15. Mood Disorders/di, pc [Diagnosis, Prevention & Control]
16. Depressive Disorder/di, pc [Diagnosis, Prevention & Control]
17. Depressive Disorder, Major/di, pc [Diagnosis, Prevention & Control]
18. Depression, Postpartum/di, pc [Diagnosis, Prevention & Control]
19. Depression/di, pc [Diagnosis, Prevention & Control]
20. validation studies.pt.
21. comparative study.pt.
22. screen*.af.
23. prevalence.af.
24. predictive value*.af.
25. detect*.ti.
26. sensitiv*.ti.
27. valid*.ti.

28. revalid*.ti.
29. predict*.ti.
30. accura*.ti.
31. psychometric*.ti.
32. identif*.ti.
33. specificit*.ab.
34. cut?off*.ab.
35. cut* score*.ab.
36. cut?point*.ab.
37. threshold score*.ab.
38. reference standard*.ab.
39. reference test*.ab.
40. index test*.ab.
41. gold standard.ab.
42. or/4-41
43. 3 and 42
44. limit 43 to yr=”2000-Current”

PsycINFO (OvidSP)

1. PHQ*.af.
2. patient health questionnaire*.af.
3. 1 or 2
4. Diagnosis/
5. Medical Diagnosis/
6. Psychodiagnosis/
7. Misdiagnosis/
8. Screening/
9. Health Screening/
10. Screening Tests/
11. Prediction/
12. Cutting Scores/

13. Psychometrics/
14. Test Validity/
15. screen*.af.
16. predictive value*.af.
17. detect*.ti.
18. sensitiv*.ti.
19. valid*.ti.
20. revalid*.ti.
21. accura*.ti.
22. psychometric*.ti.
23. specificit*.ab.
24. cut?off*.ab.
25. cut* score*.ab.
26. cut?point*.ab.
27. threshold score*.ab.
28. reference standard*.ab.
29. reference test*.ab.
30. index test*.ab.
31. gold standard.ab.
32. or/4-31
33. 3 and 32
38. Limit 33 to “2000 to current”

Web of Science (Web of Knowledge)

#1: TS=(PHQ* OR “Patient Health Questionnaire*”)

#2: TS= (screen* OR prevalence OR “predictive value*” OR detect* OR sensitiv* OR valid* OR revalid* OR predict* OR accura* OR psychometric* OR identif* OR specificit* OR cutoff* OR “cut off*” OR “cut* score*” OR cutpoint* OR “cut point*” OR “threshold score*” OR “reference standard*” OR “reference test*” OR “index test*” OR “gold standard”)

#1 AND #2

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=2000-20181.

Supplementary Table 1a. Characteristics of included primary studies (N=75)

First Author, Year	Country	Recruited Population	Diagnostic Interview	Classification System	Total N	Major Depression N (%)
Semi-structured Interviews						
Amtmann, 2015[1]	USA	Multiple sclerosis patients	SCID	DSM-IV	164	48 (29)
Ayalon, 2010[2]	Israel	Elderly primary care patients	SCID	DSM-IV	151	6 (4)
Beraldi, 2014[3]	Germany	Cancer inpatients	SCID	DSM-IV	116	7 (6)
Bernstein, 2018[4]	Canada	IBD patients	SCID	DSM-IV	240	21 (9)
Bhana, 2015[5]	South Africa	Chronic care patients	SCID	DSM-IV	679	78 (11)
Chagas, 2013[6]	Brazil	Outpatients with Parkinson's Disease	SCID	DSM-IV	84	19 (23)
Chibanda, 2016[7]	Zimbabwe	A primary care population with high HIV prevalence	SCID	DSM-IV	264	149 (56)
Fischer, 2014[8]	Germany	Heart failure patients	SCID	DSM-IV	194	11 (6)
Gräfe, 2004[9]	Germany	Medical and psychosomatic outpatients	SCID	DSM-IV	494	67 (14)
Green, 2017[10]	USA	Returning veterans	SCID	DSM-V	176	22 (13)
Green, 2018[11]	Kenya	Pregnant women and new mothers	SCID	DSM-V	192	10 (5)
Haroz, 2017[12]	Myanmar	Primary care patients	SCID	DSM-IV	132	29 (22)
Hitchon, 2019[13a]	Canada	Rheumatoid arthritis patients	SCID	DSM-IV	148	16 (11)
Khamseh, 2011[14]	Iran	Type 2 diabetes patients	SCID	DSM-IV	122	47 (39)
Kwan, 2012[15]	Singapore	Post-stroke inpatients undergoing rehabilitation	SCID	DSM-IV-TR	113	3 (3)
Lara, 2015[16]	Mexico	Pregnant women during the third trimester of pregnancy	SCID	DSM-IV	280	29 (10)
Liu, 2011[17]	Taiwan	Primary care patients	SCAN	DSM-IV	1532	50 (3)
Marrie, 2018[18]	Canada	Multiple sclerosis patients	SCID	DSM-IV	244	25 (10)

Martin-Subero, 2017[19]	Spain	Medical inpatients	SCID	DSM-III	1003	83 (8)
Osório, 2009[20]	Brazil	Women in primary care	SCID	DSM-IV	177	60 (34)
Osório, 2012[21]	Brazil	Inpatients from various clinical wards	SCID	DSM-IV	86	28 (33)
Patten, 2015[22]	Canada	Multiple sclerosis patients	SCID	DSM-IV	143	20 (14)
Picardi, 2005[23]	Italy	Inpatients with skin diseases	SCID	DSM-IV	138	12 (9)
Prisnie, 2016[24]	Canada	Stroke and transient ischemic attack patients	SCID	DSM-IV	114	11 (10)
Quinn, Unpublished[a]	UK	Stroke patients	SCID	DSM-V	135	15 (11)
Shinn, 2017[25]	USA	Cancer patients	SCID	DSM-IV	124	5 (4)
Spangenberg, 2015[26]	Germany	Primary care patients	SCID	DSM-IV	160	1 (1)
Wagner, 2017[27]	USA	Patients starting radiotherapy for the first diagnosis of any tumor	SCID	DSM-IV	54	6 (11)
Wittkampf, 2009[28]	The Netherlands	Primary care patients at risk for depression	SCID	DSM-IV	260	45 (17)
Fully Structured Interviews						
Azah, 2005[29]	Malaysia	Adults attending family medicine clinics	CIDI	ICD-10	180	30 (17)
de Man-van Ginkel, 2012[30]	The Netherlands	Stroke patients	CIDI	DSM-IV	382	54 (14)
Fisher, 2016[31]	Australia	Primiparous women less than 6 weeks postpartum	CIDI	DSM-IV	357	4 (1)
Gelaye, 2014[32]	Ethiopia	Outpatients at a general hospital	CIDI	DSM-IV	923	162 (18)
Grool, 2011[33]	The Netherlands	Non-demented patients with symptomatic atherosclerotic disease	CIDI	DSM-IV	477	22 (5)
Hahn, 2006[34]	Germany	Patients with chronic illnesses from rehabilitation centers	CIDI	DSM-IV	211	18 (9)
Henkel, 2004[35]	Germany	Primary care patients	CIDI	ICD-10	430	43 (10)
Hobfoll, 2011[36]	Israel	Jewish and Palestinian residents of Jerusalem exposed to war	CIDI	DSM-IV	144	42 (29)
Kim, 2017[37]	South Korea	Randomly selected adults	CIDI	DSM-IV	3071	205 (7)
Kohrt, 2016[38]	Nepal	Primary care patients	CIDI	DSM-IV	125	17 (14)

Liu, 2015[39]	Canada	Working population	CIDI	DSM-IV	4182	91 (2)
Mohd Sidik, 2012[40]	Malaysia	Primary care patients	CIDI	DSM-IV	146	31 (21)
Patel, 2008[41]	India	Primary care patients	CIS-R	ICD-10	299	13 (4)
Razykov, 2013[42]	Canada	Patients with systemic sclerosis	CIDI	DSM-IV	144	6 (4)
Zuithoff, 2009[43]	The Netherlands	General practice patients	CIDI	DSM-IV	1038	135 (13)
Mini International Neuropsychiatric Interviews (MINI)						
Akena, 2013[44]	Uganda	HIV/AIDS patients	MINI	DSM-IV	91	11 (12)
Baron, 2017[45]	South Africa	Xhosa, Afrikaans and Zulu-speaking general population	MINI	DSM-IV	851	93 (11)
Buji, 2018[46]	Malaysia	Patients with systemic lupus erythematosus	MINI	DSM-IV	130	5 (4)
Cholera, 2014[47]	South Africa	Patients undergoing routine HIV counseling and testing at a primary health care clinic	MINI	DSM-IV	397	47 (12)
Conway, 2016[48]	Australia	Heart transplant recipients	MINI	DSM-IV	26	2 (8)
de la Torre, 2016[49]	Argentina	Hospitalized general medical patients	MINI	DSM-IV	257	69 (27)
Garabiles, Unpublished[a]	China	Female Filipino domestic workers in Macao	MINI	DSM-IV	99	39 (39)
Gholizadeh, 2019[50a]	Iran	Coronary artery disease patients	MINI	DSM-IV	79	12 (15)
Hantsoo, 2017[51]	USA	General population	MINI	DSM-IV	321	19 (6)
Hides, 2007[52]	Australia	Injection drug users accessing a needle and syringe program	MINI	DSM-IV	103	47 (46)
Hyphantis, 2011[53]	Greece	Patients with various rheumatologic disorders	MINI	DSM-IV	213	69 (32)
Hyphantis, 2014[54]	Greece	Patients with chronic illnesses presenting at the emergency department	MINI	DSM-IV	349	95 (27)
Inagaki, 2013[55]	Japan	Internal medicine outpatients	MINI	DSM-III-R	104	21 (20)
Janssen, 2016[56]	The Netherlands	General population and Type 2 diabetes patients	MINI	DSM-IV	4695	156 (3)

Lamers, 2008[57]	The Netherlands	Elderly primary care patients with diabetes mellitus or chronic obstructive pulmonary disease	MINI	DSM-IV	104	59 (57)
Levin-Aspenson, 2017[58]	USA	General population	MINI	DSM-V	408	66 (16)
Liu, 2016[59]	China	Primary care patients	MINI	DSM-IV	1997	97 (5)
Lotrakul, 2008[60]	Thailand	Outpatients	MINI	DSM-IV	278	19 (7)
Muramatsu, 2007[61]	Japan	Primary care patients	MINI	DSM-IV	116	32 (28)
Muramatsu, 2018[62]	Japan	Primary care patients	MINI	DSM-IV	152	46 (30)
Nakku, 2016[63]	Uganda	Primary patients and hospital outpatients	MINI	DSM-IV	153	84 (55)
Paika, 2017[64]	Greece	Patients with long term medical conditions	MINI	DSM-IV	474	98 (21)
Persoons, 2001[65]	Belgium	Inpatients and patients at gastroenterological and hepatology wards	MINI	DSM-IV	173	28 (16)
Rancans, 2018[66]	Latvia	Primary care patients	MINI	DSM-IV	1467	147 (10)
Santos, 2013[67]	Brazil	General population	MINI	DSM-IV	196	25 (13)
Stafford, 2007[68]	Australia	Inpatients with coronary artery disease who had undergone surgery	MINI	DSM-IV	193	35 (18)
Sung, 2013[69]	Singapore	Primary care patients	MINI	DSM-IV	399	12 (3)
Suzuki, 2015[70]	Japan	Outpatients in general medicine department	MINI	DSM-IV	511	42 (8)
van Heyningen, 2018[71]	South Africa	Pregnant women	MINI	DSM-IV	373	81 (22)
Volker, 2016[72]	The Netherlands	Employees on sickness leave	MINI	DSM-IV	93	23 (25)
Zhang, 2013[73]	Hong Kong, China	Type 2 diabetes patients	MINI	DSM-IV	68	17 (25)

Abbreviations: CIDI: Composite International Diagnostic Interview; CIS-R: Clinical Interview Schedule Revised; DSM: Diagnostic and Statistical Manual of Mental Disorders; ICD: International Classification of Diseases; MINI: Mini Neuropsychiatric Diagnostic Interview; SCAN: Schedules for Clinical Assessment in Neuropsychiatry; SCID: Structured Clinical Interview for DSM Disorders; UK: United Kingdom; USA: United States of America.

[a]Was unpublished at the time of electronic database search

Supplementary Table 1b. Characteristics of eligible primary studies not included in the present study (N=32)

First Author, Year	Country	Recruited Population	Diagnostic Interview	Classification System	Total N	Major Depression N (%)
Semi-structured Interviews						
Alamri, 2017[74a]	Saudi Arabia	Hospitalized elderly in medical and surgical wards	SCID	DSM-IV	199	24 (12)
Bailer, 2016[75]	Germany	Healthy participants and cognitive behaviour therapy outpatients	SCID	DSM-IV	200	68 (34)
Becker, 2002[76]	Saudi Arabia	Primary care patients	SCID	DSM-III-R	173	NR[a]
Brodey, 2016[77]	USA	Perinatal women	SCID	DSM-IV	879	NR[a]
Chen, 2013[78]	China	Primary care populations	SCID	DSM-IV	280	NR[a]
Chen, 2012[79]	China	Adults over 60 in primary care	SCID	DSM-IV	262	97 (37)
Fann, 2005[80a]	USA	Inpatients with traumatic brain injury	SCID	DSM-IV	135	45 (33)
Irmak, 2017[81]	Turkey	Battered women	SCID	DSM-V	150	63 (42)
Lai, 2010[82]	China	Men with postpartum wives	SCID	DSM-IV	551	8 (1)
Limon, 2016[83]	USA	Latino farmworkers	SCID	DSM-IV	99	NR[a]
Liu, 2016[84]	China	Rural elderly population	SCID	DSM-IV	839	57 (7)
Nacak, 2017[85]	Germany	Patients with somatoform pain disorder	SCID	DSM-IV	130	36 (28)
Navinés, 2012[86]	Spain	Chronic hepatitis C patients	SCID	DSM-IV	500	32 (6)
Phelan, 2010[87]	USA	Elderly primary care patients	SCID	DSM-IV	69	8 (12)
Thompson, 2011[88]	USA	Parkinson's patients	SCID	DSM-IV	214	30 (14)
Vöhringer, 2013[89a]	Chile	Primary care patients	SCID	DSM-IV	190	59 (31)
Watnick, 2005[90]	USA	Long term dialysis patients	SCID	DSM-IV	62	12 (19)
Fully Structured Interviews						

Al-Ghafri, 2014[91]	Oman	Medical trainees	CIDI	NR	131	NR[a]
Haddad, 2013[92]	UK	Coronary heart disease patients	CIS-R	ICD-10	730	32 (4)
Ikin, 2016[93]	Australia	Veterans of the Gulf War	CIDI	DSM-IV	1356	NR[a]
Valencia-Garcia, 2017[94]	USA	Mexican American women	CIDI	DSM-IV	205	40 (20)
Wang, 2015[95]	China	Cardiovascular outpatients	CIDI	DSM-IV	201	42 (21)
Mini International Neuropsychiatric Interviews (MINI)						
Choi, 2015[96]	Canada	HIV patients	MINI	DSM-IV	190	29 (15)
Griffith, 2015[97]	USA	Patients with epilepsy	MINI	DSM-IV and ICD-10	114	20 (18)
Persoons, 2003[98]	Belgium	Otorhinolaryngology outpatients	MINI	DSM-IV	97	16 (16)
Rathore, 2014[99]	USA	Patients with epilepsy	MINI	DSM-IV	158	36 (23)
Scott, 2011[100]	USA	Chronic hepatitis C patients	MINI	DSM-IV and ICD-10	30	NR[a]
Seo, 2015[101]	South Korea	Migrane patients	MINI	DSM-IV	132	39 (30)
van Steenbergen-Weijenburg, 2010[102a]	The Netherlands	Diabetes patients	MINI	DSM-IV	196	37 (19)
Wang, 2014[103a]	China	General population	MINI	DSM-IV	1036	28 (3)
Woldetensay, 2018[104]	Ethiopia	Pregnant women	MINI	DSM-IV	216	28 (13)
Xiong, 2014[105]	China	Outpatients with multiple somatic symptoms	MINI	DSM-IV	398	116 (29)

Abbreviations: CIDI: Composite International Diagnostic Interview; CIS-R: Clinical Interview Schedule Revised; DSM: Diagnostic and Statistical Manual of Mental Disorders; ICD: International Classification of Diseases; NR: Not Reported; SCID: Structured Clinical Interview for DSM Disorders; UK: United Kingdom; USA: United States of America.

[a]Studies contributed data but were excluded for not having item scores.

Supplementary Table 1c. Characteristics of eligible primary studies included in the PHQ-dep-4 development paper (N=20)

First Author, Year	Country	Recruited Population	Diagnostic Interview	Classification System	Total N	Major Depression N (%)
Semi-structured Interviews						
Amoozegar, 2017[106]	Canada	Migraine patients	SCID	DSM-IV	203	49 (24)
Bombardier, 2012[107]	USA	Inpatients with spinal cord injuries	SCID	DSM-IV	160	14 (9)
Eack, 2006[108]	USA	Women seeking psychiatric services for their children at two mental health centers	SCID	DSM-IV	48	12 (25)
Fiest, 2014[109]	Canada	Epilepsy outpatients	SCID	DSM-IV	169	23 (14)
Gjerdingen, 2009[110]	USA	Mothers registering their newborns for well-child visits at medical or pediatric clinics	SCID	DSM-IV	419	19 (5)
Lambert, 2015[111]	Australia	Cancer patients	SCID	DSM-IV	147	21 (14)
McGuire, 2013[112]	USA	Acute coronary syndrome inpatients	DISH	DSM-IV	100	9 (9)
Richardson, 2010[113]	USA	Older adults undergoing in-home aging services care management assessment	SCID	DSM-IV	377	95 (25)
Rooney, 2013[114]	UK	Patients with cerebral glioma	SCID	DSM-IV	126	14 (11)
Sidebottom, 2012[115]	USA	Pregnant women	SCID	DSM-IV	246	12 (5)
Simning, 2012[116]	USA	Older adults living in public housing	SCID	DSM-IV	190	10 (5)
Turner, 2012[117]	Australia	Stroke patients	SCID	DSM-IV	72	13 (18)
Turner, Unpublished[a]	Australia	Cardiac rehabilitation patients	SCID	DSM-IV	51	4 (8)
Twist, 2013[118]	UK	Type 2 diabetes outpatients	SCAN	DSM-IV	360	80 (22)
Williams, 2012[119]	USA	Parkinson's Disease patients	SCID	DSM-IV	235	61 (26)
Fully Structured Interviews						

Arroll, 2010[120]	New Zealand	Primary care patients	CIDI	DSM-IV	2528	156 (6)
Delgadillo, 2011[121]	UK	Injecting drug users	CIS-R	ICD-10	103	51 (50)
Kiely, 2014[122]	Australia	Community sample of adults	CIDI	ICD-10	822	33 (4)
Pence, 2012[123]	Cameroon	HIV-infected patients	CIDI	DSM-IV	398	11 (3)
Thombs, 2008[124]	USA	Outpatients with coronary artery disease	C-DIS	DSM-IV	1006	221 (22)

Abbreviations: C-DIS: Computerized Diagnostic Interview Schedule; CIDI: Composite International Diagnostic Interview; CIS-R: Clinical Interview Schedule Revised; DISH: Depression Interview and Structured Hamilton; DSM: Diagnostic and Statistical Manual of Mental Disorders; ICD: International Classification of Diseases; MINI: Mini Neuropsychiatric Diagnostic Interview; SCAN: Schedules for Clinical Assessment in Neuropsychiatry; SCID: Structured Clinical Interview for DSM Disorders; UK: United Kingdom; USA: United States of America.

[a]Was unpublished at the time of electronic database search

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