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1 ***Probability of Major Depression Classification Based on the SCID, CIDI and MINI***
2 ***Diagnostic Interviews: A Synthesis of Three Individual Participant Data Meta-Analyses***

3
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COMPARISON OF DIAGNOSTIC INTERVIEWS FOR MAJOR DEPRESSION

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43

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44 **ABSTRACT**

45 **Objective:** To compare odds of major depression classification based on the Structured Clinical Interview
46 for DSM (SCID), the Composite International Diagnostic Interview (CIDI), and the Mini International
47 Neuropsychiatric Interview (MINI).

48 **Methods:** We included and standardized data from three individual participant data meta-analysis (IPDMA)
49 databases, which included primary studies with depressive symptom scores from the Patient Health
50 Questionnaire-9, Edinburgh Postnatal Depression Scale, or Hospital Anxiety and Depression Scale –
51 Depression subscale plus diagnostic interview-based major depression status. For each IPDMA, separately,
52 we fit binomial generalized linear mixed models to compare adjusted odds ratios (aORs) of (1) major
53 depression classification, controlling for depression symptom severity and participant characteristics, and
54 (2) the interaction between interview and symptom severity. Next, we synthesized results using
55 DerSimonian-Laird random-effects meta-analysis.

56 **Results:** In total, 69,405 participants (7,574 [11%] with major depression) from 212 studies were included.
57 Controlling for symptom severity and participant characteristics, the MINI (74 studies; 25,749 participants)
58 classified major depression more often than the SCID (108 studies; 21,953 participants; aOR [95% CI] =
59 1.46 [1.11-1.92]). Classification odds for the CIDI (30 studies; 21,703 participants) and SCID did not differ
60 overall (aOR [95% CI] =1.19 [0.79, 1.75]), but as screening scores increased, aOR increased less for the
61 CIDI than the SCID (interaction aOR [95% CI] = 0.64 [0.52-0.80]).

62 **Conclusions:** Compared to the SCID, the MINI classified major depression more often. Odds of depression
63 classification with the CIDI increased less as symptom levels increased. Interpretation of research that uses
64 diagnostic interviews to classify depression should consider interview characteristics.

65

66 **INTRODUCTION**

67 In mental health research, diagnostic interviews are used to classify disorders in a manner consistent
68 with standard classification systems and replicable across studies [1-4]. There are important differences,
69 however, in the designs of commonly used interviews. Semi-structured interviews are designed for
70 administration by trained professionals with diagnostic experience; evaluators can interject queries and use
71 their clinical judgment to determine whether symptoms are present and significant [1-3]. The Structured
72 Clinical Interview for DSM (SCID) [4] is the most commonly used semi-structured interview in depression
73 research [5-7]. Fully structured interviews, in contrast, are designed for lay interviewer administration to
74 reduce the cost of clinician-administered interviews. They are completely scripted, and evaluators cannot
75 provide additional explanations or rephrase questions; minimal judgment is involved. They are intended to
76 maximize reliability but may reduce validity [8]. The Composite International Diagnostic Interview (CIDI)
77 [8] is the most commonly used fully structured interview for depression research [5-7]. The Mini
78 International Neuropsychiatric Interview (MINI) [9,10], also common in depression research, is a very brief
79 fully structured interview, originally described by its developers as a screening interview and intended to be
80 over-inclusive [10].

81 Despite their differences, semi-structured interviews, fully structured interviews of conventional
82 length, and abbreviated alternatives such as the MINI are usually treated as equivalent. For instance, meta-
83 analyses of depression screening tool accuracy typically pool primary study results without consideration of
84 reference standards [11-17]. Until recently, however, only several small studies, each with 61 depression
85 cases or fewer, compared classification by different diagnostic interviews [2,18-23]. Recently, three
86 individual participant data meta-analyses (IPDMA) compared odds of major depression classification
87 between different diagnostic interviews, controlling for depression symptom severity scores and participant
88 characteristics [5-7]. Those included an IPDMA with 17,158 participants from 57 primary studies that used
89 the Patient Health Questionnaire-9 (PHQ-9) to control for depression symptom severity [5], 12,759 women

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90 in pregnancy or postpartum from 46 studies that used the Edinburgh Postnatal Depression Scale (EPDS) [6],
91 and 15,856 participants from 73 studies that used the depression subscale of the Hospital Anxiety and
92 Depression Scale (HADS-D) [7]. Results suggested that, compared to semi-structured interviews (e.g.,
93 SCID) [4], the CIDI may classify more people with relatively low-level symptoms as depressed but fewer
94 people with higher symptom levels. The MINI appeared to classify major depression in more people across
95 the symptom spectrum. There was important imprecision in results, however, including wide confidence
96 intervals (CIs) around estimates.

97 Our objective was to synthesize results from three separate IPDMAs datasets to and compare the most
98 commonly used diagnostic interviews for major depression, the SCID, CIDI, and MINI to determine (1) if
99 odds ratios for major depression classification using the CIDI and MINI differ from the SCID, controlling
100 for depression symptom severity and participant characteristics, and (2) if there is an interaction between the
101 interview and depressive symptom level that would suggest that differences in classification odds are
102 associated with symptom levels.

103 **MATERIALS AND METHODS**

104 We conducted a two-stage evidence synthesis. We first conducted IPDMAs in the PHQ-9, EPDS, and
105 HADS datasets, separately, by fitting models with and without interaction terms for depressive symptom
106 severity in each dataset, separately. Second, we pooled estimates from the results of the three IPDMAs.

107 **Inclusion Criteria for the Included Datasets**

108 For the PHQ-9, EPDS, and HADS-D IPDMAs, datasets from articles in any language were eligible
109 for inclusion if (1) they included diagnostic classification for current Major Depressive Disorder or Major
110 Depressive Episode using Diagnostic and Statistical Manual of Mental Disorders [24-27] or International
111 Classification of Diseases [28] criteria based on a validated semi-structured or fully structured interview; (2)
112 they included PHQ-9, EPDS, or HADS-D scores; (3) the diagnostic interview and depression screening test
113 were administered within two weeks of each other; and (4) participants were ≥ 18 years, not recruited from

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114 youth or college settings, and not recruited from psychiatric settings or because a screening test identified
115 them as having symptoms of depression [29-31]. For the EPDS, participants were women in pregnancy or
116 within 12 months postpartum [30]. In each IPDMA, datasets where not all participants were eligible were
117 included if primary data allowed selection of eligible participants [29-31]. Over 90% of all included studies
118 in the IPDMA databases used the SCID, CIDI, or MINI diagnostic interviews. Thus, for the present study,
119 as we did in the published IPDMAs of the EDPS [6] and HADS-D [7], we restricted analyses to studies that
120 used SCID, CIDI, or MINI.

121 **Search Strategy, Study Selection, Data Acquisition, and Data Extraction**

122 For more details on the search and selection processes, as well as data contribution, extraction, and
123 synthesis, please see Supplementary Method 1. For information on how the IPDMA datasets and the
124 analyses conducted in the present study deviated from our previous published IPDMAs on diagnostic
125 interview performance using the PHQ-9 [5], EPDS [6], and HADS-D [7] IPDMA databases, please see
126 Supplementary Method 2, Supplementary Method 3, and Supplementary Figure 1.

127 **Statistical Analysis**

128 *IPDMAs of PHQ-9, EPDS, and HADS-D Datasets:*

129 We initially standardized symptom severity scores in each dataset. To do this, for each measure, we
130 converted raw screening tool scores to standardized scores by Z-transformation (subtracting the mean and
131 dividing by the standard deviation of raw scores). We then meta-analyzed the PHQ-9, EPDS, and HADS
132 datasets, separately. In each dataset, we fit binomial generalized linear mixed models with a logit link
133 function to compare the adjusted odds ratio (aOR) of major depression classification for the CIDI versus the
134 SCID, the MINI versus the SCID, and, as a supplementary analysis, the MINI versus the CIDI, controlling
135 for depressive symptom levels and other participant characteristics. We adjusted for different covariates in
136 the models for each dataset, based on relevant measures. For the PHQ-9 and HADS-D datasets, as in the
137 previously published IPDMAs [5,7], we controlled for depressive symptom severity (continuous

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138 standardized scores), age, sex, country Human Development Index (very high, high, or low-medium) [32],
139 and patient care setting (PHQ-9: primary care, outpatient specialty care, inpatient specialty care, non-
140 medical care [33]; HADS-D: outpatient care, inpatient care, non-medical care, mixed inpatient and
141 outpatient [7]). For the EPDS, we did not control for sex or patient care settings but controlled for
142 pregnancy versus postpartum status [6]. To account for the correlation between subjects within primary
143 studies in each dataset, a random intercept was fit. Fixed slopes were estimated for all covariates in each
144 model. We also fit additional models in each dataset, where we added an interaction term between interview
145 and depressive symptom severity (continuous PHQ-9, EPDS, and HADS-D standardized scores), to
146 evaluate whether any differences in aOR of major depression classification were associated with depression
147 symptom severity.

148 *Synthesis of IPDMA Results:*

149 To synthesize results from the three IPDMAs, we pooled estimates of the aOR for each comparison
150 (CIDI versus SCID, MINI versus SCID, MINI versus CIDI) and the aOR for the interaction of interview
151 and depression symptom severity in each comparison, along with 95% CIs. We used DerSimonian-Laird
152 random effects meta-analysis to pool the aORs [34]. Heterogeneity was examined using the I^2 statistic based
153 on log aORs [35]. Because some studies were included in both the PHQ-9 and HADS-D IPDMAs, as a
154 sensitivity analysis, we re-analyzed results after removing those studies.

155 All analyses were conducted in R (R version R 3.5.1 and R Studio version 1.1.463) [36,37] using the
156 glmer function within the lme4 package [38] and the rma function within the metafor package [39].

157 **RESULTS**

158 In total, 69,405 participants (7,574 [11%] with major depression) were included in the three individual
159 IPDMAs (Table 1). Of the 212 included primary studies, the SCID was used in 108 studies (21,953
160 participants, 14% major depression), the CIDI in 30 studies (21,703 participants, 7% major depression), and
161 the MINI in 74 studies (25,749 participants, 12% major depression). Mean (standard deviation) of raw

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162 screening tool scores, prior to standardization, were 4.99 (5.26) for the PHQ-9, 6.98 (5.58) for the EPDS,
163 and 5.16 (4.07) for the HADS-D. Characteristics of individual primary studies are available in
164 Supplementary Table 1 with details for PHQ-9 update in Supplementary Method 1. There were 13 studies
165 that were included in both the PHQ-9 and HADS-D datasets, including 2,383 (6%) participants in the PHQ-
166 9 IPDMA and 2,349 participants (15%) in the HADS-D IPDMA. There was no overlap between the EPDS
167 and the PHQ-9 or HADS-D IPDMAs.

168 Estimates of aORs of major depression classification by diagnostic interview, controlling for
169 depressive symptom severity and other participant characteristics, individually and pooled, are reported in
170 Table 2. Overall odds of major depression classification did not differ for the CIDI versus the SCID (aOR
171 1.19, 95% CI = 0.79 to 1.75) in the full model that included the interaction term, but there was a significant
172 interaction between the CIDI and depressive symptom severity; as screening tool scores increased, odds of
173 major depression classification increased less for the CIDI than for the SCID (interaction aOR = 0.64, 95%
174 CI = 0.52 to 0.80). As shown in Figure 1, participants with lower depressive symptom severity were more
175 likely to be classified with major depression with the CIDI compared to the SCID, but the opposite was true
176 with greater symptom severity. Compared to the SCID, the MINI classified major depression more often
177 (aOR 1.45; 95% CI = 1.08 to 1.93), controlling for depressive symptom severity and participant
178 characteristics. There was no apparent interaction between symptom levels and odds of classification
179 (interaction aOR = 0.95, 95% CI = 0.78 to 1.15). See Figure 2.

180 Trends of the probability of major depression classification by reference standards for individual
181 IPDMAs are presented in Supplementary Figures 2-4. There was minimal between-IPDMA heterogeneity in
182 overall aORs for the comparison of the CIDI versus the SCID and the MINI versus the SCID in models
183 without the interaction term ($I_2 = 11\%$ and 0% , respectively) and including the interaction term ($I_2 = 0\%$ and
184 0% , respectively). However, there was substantial between-IPDMA heterogeneity of interaction aORs for
185 both comparisons ($I_2 = 82\%$ and 82%). See Table 2.

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186 In the comparison of the MINI versus the CIDI, the MINI was more likely to classify participants as
187 having major depression than the CIDI (aOR = 2.05; 95% CI = 1.36 to 2.10), controlling for depressive
188 symptom levels and other participant characteristics. As screening tool scores increased, the odds of major
189 depression classification increased more for the MINI than for the CIDI (interaction aOR = 1.48, 95% CI =
190 1.36 to 1.60). Heterogeneity was low for aORs with and without the interaction term, and interaction aORs
191 ($I_2 = 0\%$, 0% , and 0%).

192 In the individual IPDMAs, some results from the EPDS dataset appeared to diverge from those
193 generated in the PHQ-9 and HADS-D datasets. However, the number of studies and cases included in the
194 EPDS dataset for the CIDI and MINI were smaller than any other combination of screening tool and
195 diagnostic interview. See Table 1.

196 As a sensitivity analysis, we removed the 13 datasets that were included in both the PHQ-9 and
197 HADS-D IPDMAs and re-ran all analyses. Results were similar (see Supplementary Table 2).

198 **DISCUSSION**

199 There were two main findings. First, overall odds of major depression classification did not differ
200 between the fully structured CIDI and the semi-structured SCID. However, adjusting for depressive
201 symptom levels and participant characteristics, odds of major depression classification with the CIDI
202 increased significantly less than for the SCID as depressive symptom levels increased. This suggests that,
203 compared to the SCID, the CIDI is relatively more likely to classify individuals with subthreshold or mild
204 depressive symptoms and relatively less likely to classify people with more severe symptoms. Second,
205 participants evaluated with the MINI were significantly more likely to be classified as having major
206 depression compared to those assessed with the SCID, independent of symptom severity. Between-study
207 heterogeneity was low for models without the interaction term, but higher for models with interaction terms.
208 Estimates from the EPDS IPDMA appeared to diverge somewhat from the PHQ-9 and HADS-D IPDMAs.

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209 This may have been related to the small numbers of studies and major depression cases for the CIDI and
210 MINI among studies that used the EPDS.

211 Our findings appear to be consistent with characteristics of the different types of diagnostic
212 interviews. The MINI was designed as a screening interview and described by its developers as over-
213 inclusive in classifying psychiatric disorders [10]. For the CIDI, the lack of sensitivity to different levels of
214 depressive symptoms severity may be because the CIDI assesses symptoms in the last 12 months and over
215 the lifetime, then probes to determine if those symptoms are currently present using only a single question.
216 In contrast, the SCID and the MINI specifically assess symptoms in the past two weeks. In addition, the
217 CIDI is much more complicated than the MINI or the SCID. It includes complex branches and is scored
218 using algorithms subject to calibration, which may influence how well diagnoses map onto DSM criteria.
219 This could lead to error at all symptom levels, which would result in more people classified at lower
220 symptom severity levels and fewer at higher levels.

221 Results were generally consistent with limited evidence from small studies that previously directly
222 compared depression classification by administering semi- and fully structured diagnostic interviews to the
223 same participants. In two studies that examined general population samples with low prevalence, fully
224 structured interviews classified major depression substantially more frequently than semi-structured
225 interviews [2,20]. On the other hand, in a study of participants in inpatient alcohol treatment, where
226 symptom severity would be expected to be higher, depression classification likelihood was similar with
227 semi-structured and fully structured interviews [22].

228 Our findings have important implications for research, including clinical trials, prognostic and risk
229 factor studies, diagnostic accuracy studies, and prevalence studies. Concerns have been raised about the
230 degree to which antidepressant trials are generalizable to real-world clinical practice [40]. Based on our
231 findings, the method used to classify depression status is also an important consideration. If used to
232 determine trial eligibility, the CIDI may not identify some participants who would be eligible based on the

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233 SCID, whereas both CIDI and MINI may include some participants who would not be eligible based on the
234 SCID, which could reduce the ability to detect treatment effects and further limit applicability to
235 participants in practice who meet diagnostic criteria. Differences in classifying participants could similarly
236 reduce the ability to identify potential associations between risk factors and depression. In diagnostic test
237 accuracy studies, depression screening tool accuracy has been shown to differ across reference standards
238 [33,41,42]. In studies of major depression prevalence, the MINI will overestimate compared to the SCID,
239 whereas with the CIDI, relative prevalence will depend on the underlying distribution of depressive
240 symptoms.

241 Our findings, which are contrary to the common belief that different reference standards can be
242 treated equivalently in mental health research, provide evidence that different approaches are needed [43].
243 Ideally, researchers would use semi-structured interviews, such as the SCID, which are designed to replicate
244 diagnostic procedures as closely as possible, to establish diagnostic status. However, this is not always
245 feasible due to the resources required, including highly trained staff. Future studies are needed to develop
246 models to calibrate weights of major depression classification based on different reference standards that
247 could facilitate synthesis of results using different diagnostic interviews. Meanwhile, in selecting a
248 diagnostic interview for use in research, investigators should consider advantages and disadvantages of
249 different interviews, including performance characteristics and resources required. In published studies,
250 authors should comment on potential implications of the type of diagnostic interview that was used. Users
251 of research, including clinicians, should be aware that results from studies that use the CIDI or MINI may
252 differ from what would be found using semi-structured interviews, which are designed to replicate
253 diagnostic procedures as closely as possible. It is also important to underline that from a clinimetric
254 perspective [44-46], assessment of diagnostic status alone is not sufficient, but that rating tools and self-
255 report questionnaires are needed to characterize symptom severity and the specific nature of experienced
256 symptoms.

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257 A strength of the present study was the inclusion of 69,405 participants with 7,574 (11%) major
258 depression cases from 212 studies. This allowed us to overcome limitations of previous IPDMAs and
259 generate more precise estimates. A second strength was that data within each included dataset were
260 standardized in terms of definitions of major depression classification, eligibility criteria, and variables. A
261 limitation to consider is that for included IPDMAs, we could not obtain primary data for 28 of 117 eligible
262 PHQ-9 studies (24% of eligible studies, 17% of eligible participants), 19 of 64 EPDS studies (30% of
263 eligible studies, 30% of eligible participants), and 47 of 116 HADS-D studies (41% of eligible studies, 29%
264 of eligible participants). A second is that we used standardized scores instead of raw depression symptom
265 scores, which required making the assumption that a standard deviation change in scores was equivalent
266 across different screening tools. Third, because only three estimates were pooled, our ability to estimate
267 heterogeneity and explore possible causes was limited. Fourth, some studies were included in both the
268 PHQ-9 and HADS-D IPDMAs. However, a sensitivity analysis showed that results were similar when these
269 studies were removed. Fifth, we examined the SCID, CIDI, and MINI, because we did not have access to
270 enough studies to include other diagnostic interviews. It is unclear to what degree our findings would
271 generalize to other diagnostic interviews. Finally, our study did not include a head-to-head comparison of
272 interviews from a randomized controlled trial or by administering different interviews to all participants. It
273 is unlikely, however, that such a study would be feasible with a large enough sample to draw conclusions
274 with confidence. Our study design, despite its limitations, overcame this barrier.

275 To conclude, the semi-structured SCID was designed to replicate diagnostic standards and procedures
276 as closely as possible. By synthesizing results from three large IPDMAs, we found that the most commonly
277 used fully structured diagnostic interviews to classify major depression, the CIDI and MINI, did not
278 perform equivalently to the SCID. The CIDI is not as responsive as the SCID to different levels of reported
279 depressive symptoms, and the MINI identifies more cases across the spectrum of depressive symptom
280 levels. Researchers should carefully consider the advantages and disadvantages of using these diagnostic

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281 interviews, and findings from studies based on the CIDI or the MINI should be interpreted considering how
282 their performance deviates from that of the SCID.

283

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285

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289 and interpretation. YW, AB and BDT contributed to drafting the manuscript. All authors provided a critical
290 review and approved the final manuscript. AB and BDT are the guarantors; they had full access to all the
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701 **FIGURE LEGENDS**

702
703 **Figure 1.** Comparison of major depression classification odds of the Composite International Diagnostic
704 Interview (CIDI) versus the Structured Clinical Interview for DSM (SCID)

705
706 The figure presents the aOR of major depression classification for the CIDI compared to the SCID for
707 primary studies based on the PHQ-9, EPDS, and HADS-D and pooled estimates at standardized scores of -
708 1, 0, 1, 2 and 3. The standardized scores of -1, 0, 1, 2 and 3 are approximately equal to scores of 0, 5, 10, 16
709 and 21 on the PHQ-9 (SD = 5.26); 1, 7, 13, 18 and 24 on the EPDS (SD = 5.58); and 1, 5, 9, 13 and 17 on
710 the HADS-D (SD = 4.07). We present standardized scores from -1 to 3, because raw scores corresponding
711 to standardized scores below -1 or above 3 would be negative or beyond the maximum scores of the
712 included screening tools.

713
714 Abbreviations: EPDS: Edinburgh Postnatal Depression Scale; HADS-D: Depression subscale of Hospital
715 Anxiety and Depression Scale; META: Pooled estimates from the synthesis meta-analysis. PHQ-9: Patient
716 Health Questionnaire-9.

COMPARISON OF DIAGNOSTIC INTERVIEWS FOR MAJOR DEPRESSION

719 **Figure 2.** Comparison of major depression classification odds of the Mini International Neuropsychiatric
720 Interview (MINI) vs. the SCID considering the interaction between depressive symptom severity and the
721 MINI

722

723 The figure presents the aOR of major depression classification for the MINI compared to the SCID for
724 primary studies based on the PHQ-9, EPDS, and HADS-D and pooled estimates at standardized scores of -
725 1, 0, 1, 2 and 3. The standardized scores of -1, 0, 1, 2 and 3 are approximately equal to scores of 0, 5, 10, 16
726 and 21 on the PHQ-9 (SD = 5.26); 1, 7, 13, 18 and 24 on the EPDS (SD = 5.58); and 1, 5, 9, 13 and 17 on
727 the HADS-D (SD = 4.07). We present standardized scores from -1 to 3, because raw scores corresponding
728 to standardized scores below -1 or above 3 would be negative or beyond the maximum scores of the
729 included screening tools.

730

731 Abbreviations: EPDS: Edinburgh Postnatal Depression Scale; HADS-D: Depression subscale of Hospital
732 Anxiety and Depression Scale; META: Pooled estimates from the synthesis meta-analysis. PHQ-9: Patient
733 Health Questionnaire-9.

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