

1 **Optimizing cognitive and behavioural approaches for perinatal**
2 **depression: a systematic review and meta-regression analysis**

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Optimizing cognitive and behavioural approaches for perinatal depression: a systematic review and meta-regression analysis

Abstract

Cognitive behavioural therapies (CBT) have been demonstrated efficacious in treating perinatal depression (PND). This has been demonstrated in several meta-analyses of randomized controlled trials and quasi-experimental studies. However, there is a need for up-to-date meta-analytical evidence providing reliable estimates for CBT's effectiveness in treating and preventing PND. Furthermore, with the world moving towards precision medicine, approaches require a critical synthesis of psychotherapies, especially to unpack their mechanisms of action and to understand what approaches work best for whom. Therefore, the present systematic review and meta-regression analyses aim to answer these research questions.

We searched six academic databases through February 2022 and identified 56 studies for an in-depth review. Using pretested data extraction sheets, we extracted patient-level and intervention-level characteristics and effect size data from each study. Random effects meta-analyses and mixed effect subgroup analyses were run to delineate the effectiveness and moderators of CBT interventions for PND, respectively. CBT based interventions yielded a strong effect size (SMD= -0.74, 95% CI: -0.91 to -0.56, n= 9,722) in alleviating depressive symptoms. These interventions were effective across different delivery formats (individual, group, and electronic) and could be delivered effectively by specialists and non-specialists. Longer duration CBT interventions may not necessarily be more effective than shorter ones. Moreover, CBT-based interventions should consider including various behavioural ingredients to maximize intervention benefits.

Keywords: Cognitive behavioural therapy, CBT, perinatal depression

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Impact statement

53 Perinatal depression is very prevalent worldwide. It is associated with poor maternal and infant health
54 outcomes and thus, a significant public health concern. Cognitive behavioural (CB) therapy is an
55 evidence-based and one of the most effective treatments for perinatal depression. This systematic
56 review and meta-analysis provide an overview of interventional research testing different cognitive
57 behavioural approaches for perinatal depression. It synthesizes findings about the development of CB-
58 based approaches delivered either individually, in groups or electronically. Thereafter, using
59 established frameworks, this review also dissects the interventions into their components.
60 Quantitative evidence is provided regarding the factors which could improve or worsen the efficacy of
61 these interventions. These include but are not limited to characteristics of women undergoing CB
62 treatment, the format of delivery and approaches utilized in these intervention programmes. It is
63 hoped that this synthesis of literature would guide researchers, clinicians and implementors in better
64 delivery of CB approaches for perinatal depression in different settings.

65 **1.1. Background**

66 Perinatal depression (PND) is a public health priority due to its high prevalence and ill effects on child
67 health (Anderson et al., 2017; Bowers et al., 2021; Gelaye et al., 2016; Husain et al., 2006). It is one
68 of the most common mental disorders among perinatal women and is studied widely in low and
69 middle-income countries (LMIC) (Gelaye et al., 2016). In LMIC, around 25.3% of antenatal women
70 and 19% of postpartum women report depressive symptoms (Gelaye et al., 2016). Women with PND
71 are at a higher risk of developing perinatal complications, including intrauterine growth retardation,
72 preterm deliveries, low birth weight, and infectious illnesses among their infants (Gelaye et al., 2016).
73 In addition, untreated PND affects child health postnatally, leading to poorer growth,
74 neurodevelopmental, socioemotional, and academic outcomes (Ashman et al., 2008; Bao et al., 2016;
75 Betts et al., 2015; Bowers et al., 2021; Chae et al., 2020; Dubowitz et al., 2002; Fanti and Kimonis,
76 2017; Netsi et al., 2018). Therefore, strategies to address maternal mental health is increasingly
77 becoming the focus of maternal and child public health initiatives, especially in LMIC (Rahman et al.,
78 2018; Rahman et al., 2008; Sikander et al., 2019a; Sikander et al., 2019b).

79 Fortunately, efficacious preventive and treatment interventions exist for PND in the form of
80 psychological and psychosocial therapies (Li et al., 2022; Rahman et al., 2018; Sockol, 2015; Waqas
81 et al., 2022b). Experimental evidence, however, is still lacking for pharmacotherapies for PND
82 (Brown et al., 2021; Howard and Khalifeh, 2020). Several meta-analyses of randomized controlled
83 trials (RCTs) have repeatedly shown that cognitive behavioural therapies (CBT) are among the most
84 efficacious treatments for PND (Li et al., 2022; Rahman et al., 2018; Sockol, 2015; Waqas et al.,
85 2022b). For instance, strong effect sizes were reported for CBT based treatment interventions for
86 PND (SMD= 0.65, 95% CI: 0.54–0.76) (Sockol, 2015). While CBT interventions have yielded weak
87 to moderate strength effect sizes in the prevention of PND (SMD=0.39, 95%CI: 0.17–0.60) (Sockol,
88 2015). These therapies are also acceptable among the stakeholders and end-consumers in LMIC and,
89 thus, suitable for large-scale implementation (Rahman et al., 2018).

90 Research evidence demonstrates CBT interventions' adequate effectiveness, utility, and
91 implementation (Li et al., 2022; Rahman et al., 2018; Sockol, 2015; Waqas et al., 2022b). However,
92 there is a paucity of evidence delineating what works and for whom. Answering these questions is
93 important to optimize psychotherapies for different populations, for example, by choosing the right
94 treatments for the right candidates (Delgadillo et al., 2022). An increasing body of research has shown
95 that these treatments work in different settings (Sockol, 2015). However, there is little research
96 evidence on how and for whom these interventions work (Cuijpers et al., 2019; Furukawa et al.,
97 2021). Thus, delineating the mechanistic pathways of different psychotherapeutic treatments has
98 gained priority in the research agenda for depression (Huibers et al., 2020). Mediation research is an
99 important tool to understand how psychotherapies work, while prediction and moderation research

100 help identify for whom these interventions work (Huibers et al., 2020). Using these tools, we can
101 attempt to unpack the black box of psychological therapies, a challenge for the field identified as early
102 as 1967 by Paul (Huibers et al., 2020; Paul G, 1967).

103 More recently, two complementary research streams in psychotherapy have emerged: one that focuses
104 on harmonizing terminology across different schools of psychotherapies (Chorpita et al., 2005;
105 Chowdhary et al., 2014; Singla et al., 2017), and the other focuses on empirical causal processes of
106 change brought about by psychological interventions (Singla et al., 2021). Important research in the
107 former domain includes the works of Chorpita et al. (Chorpita et al., 2005) and Abraham & Michie
108 (Abraham and Michie, 2008), who sought to harmonize the taxonomy of treatment strategies utilized
109 across different psychotherapies. Based on this work, researchers have posited that there are
110 commonalities between different forms of psychotherapies. While having different theoretical
111 underpinnings, these psychotherapies may work through similar mechanisms.

112 Two classes of therapeutic ingredients of psychotherapies have been posited: specific and non-
113 specific or common ingredients (Singla et al., 2017). Specific active ingredients emerge from the
114 theoretical models of different psychotherapies. For instance, cognitive behavior therapy is based on
115 cognitive theory and hypothesized to work through challenging and changing maladaptive thought
116 patterns or cognitive schemas, while behavioural therapies work by correcting maladaptive behaviors.
117 Similarly, interpersonal psychotherapy is hypothesized to act through interpersonal change
118 mechanisms (Chorpita et al., 2005; Cuijpers et al., 2019; Huibers et al., 2020; Kahl et al., 2012).
119 Whereas common ingredients or elements include techniques used by therapists during the delivery of
120 therapy sessions, e.g., building rapport and empathy or helping the client to identify sources of social
121 support. These common active ingredients are shared across all forms of psychotherapy. Rosenzweig
122 cites these common ingredients as the primary reason for comparable effect sizes across different
123 psychotherapies (Eysenck, 1955; Rosenzweig, 1936).

124 Even after decades of research, none of the theories has yielded conclusive empirical evidence, and
125 the black box of psychotherapies remains unpacked. Moreover, there is also a paucity of evidence on
126 optimizing and personalizing treatment with psychotherapies. Therefore, the present systematic
127 review and meta-regression analysis aims to:

- 128 i. Assess the effectiveness of CBT-based interventions for prevention and treatment of PND
- 129 ii. Explore the settings in which these interventions work the best.
- 130 iii. Explore the individual level and intervention level factors driving PND's prognosis among
131 women undergoing CBT.
- 132 iv. Explore the active ingredients of CBT interventions for PND.

133

134 **1.2. Methods**

135 **1.2.1. Search strategy**

136 This systematic review and meta-analysis have been conducted per the PRISMA guidelines (Page et
137 al., 2021). Before the conduct of this review, its protocol was registered on the PROSPERO database
138 (Waqas and Rahman, 2022). The current systematic review does not report findings concerning
139 secondary outcomes mentioned in the PROSPERO protocol. Using a pretested search strategy
140 (Supplementary Table 1), we searched six academic databases, including PubMed, Medline, Web of
141 Science, Psycinfo, Cochrane central registry of trials, and CINAHL, through February 2022.

142 **1.2.2. Inclusion & Exclusion criteria**

143 We included all randomized and cluster randomized controlled trials that reported the effectiveness of
144 cognitive, behavioural, and third-wave psychotherapeutic interventions as standalone or as part of
145 complex multicomponent interventions (Supplementary Table 2). We included cognitive and
146 behavioural therapy-based interventions for perinatal depression, delivered during the antenatal period
147 and up to 1-year postnatal. Those trials were considered that reported either the rate of perinatal
148 depression or symptom severity of perinatal depressive symptoms as a primary outcome. Preventive
149 interventions were considered for both indicated (populations with prodromal symptoms) and targeted
150 (at-risk) populations. While for treatment interventions, we included those which recruited perinatal
151 women who were either screened positive for perinatal depression using psychometric scales or
152 diagnosed clinically using ICD or DSM clinical diagnostic criteria. Interventions conducted among
153 peripartum women with medical comorbidities were also considered. When available, we also
154 reviewed intervention manuals and secondary publications associated with the eligible randomized
155 controlled trials. This was done to aid in synthesizing evidence on the active ingredients of CBT
156 interventions.

157 We excluded studies that did not report perinatal depression (rates of diagnoses or severity of
158 symptoms) as an outcome. We also excluded studies not available in the English language and short
159 formats of publications such as brief reports, letters to editors, conference papers and abstracts.

160

161 **1.2.3. Outcomes**

162 As primary outcomes, we considered on either rate of PND assessed using clinical criteria of
163 diagnoses or scores on valid and reliable psychometric scales; assessed post-intervention. This review
164 does not report findings pertaining to secondary outcomes outlined in the PROSPERO protocol.

165 **1.2.4. Study selection procedures and data extraction**

166 Teams comprising two independent reviewers screened database records against inclusion and
167 exclusion criteria using a two-phased approach (titles and abstracts followed by full texts). After
168 identification of studies fulfilling the eligibility criteria, data on characteristics of intervention and

169 study samples were extracted. Study level characteristics included the year of publication, study
170 design, type of control group, and inclusion and exclusion criteria. While patient-level characteristics
171 included mean age, the proportion of participants belonging to minority ethnic groups and lower
172 income class, parity, family structure, and intervention timing (antenatal or gestational age if
173 available, or postpartum period). We also catalogued intervention-level characteristics such as the
174 scope of the intervention (targeted prevention, indicated prevention, and treatment), the theoretical
175 underpinning of interventions, the format of delivery (individual, group, electronic), setting of
176 intervention, delivery agent (specialist and non-specialist) and the number of sessions of intervention.
177 These variables were selected a priori as described in the systematic review protocol (Waqas and
178 Rahman, 2022).

179 **1.2.5. Taxonomy of interventions: Distillation & Matching framework**

180 This exercise was done to delineate different elements and active ingredients of cognitive behavioural
181 interventions included in this review. It is based on the premise that interventions to improve mental
182 health are varied and may comprise: i) a combination of specific or non-specific active ingredients
183 underpinned by a single theory-based approach, often called a therapy (e.g., CBT) or ii) a combination
184 of elements drawn from different theories, forming a multicomponent intervention or eclectic therapy.
185 An additional complication is that multi-component interventions usually comprise ingredients that
186 may be derived from another discipline, e.g., CBT may be delivered in tandem exercise or yoga. All
187 this creates a problem for the field as it is important for policymakers to know which interventions
188 provide the best evidence for effectiveness and feasibility (Abraham and Michie, 2008; Chorpita et
189 al., 2005; Cuijpers et al., 2019; Furukawa et al., 2021; Huibers et al., 2020; Michie et al., 2013).
190 Furthermore, it also complicates the understanding of mediational or causal mechanisms that drive an
191 intervention's efficacy.

192 To decompose the CBT-based interventions into their components or active ingredients, we utilized
193 the distillation and matching framework for psychotherapies devised by Chorpita et al. (2005). This
194 approach was further informed by Michie and colleagues' hierarchically clustered taxonomy of
195 behaviour change techniques (Abraham and Michie, 2008; Michie et al., 2013). These frameworks
196 were used to harmonize the definitions of active ingredients across the studies included in this review.
197 To devise a hierarchal taxonomy suitable for this review, we used the definitions proposed by the
198 Institute of Medicine's framework for psychotherapies (England et al., 2015). The hierarchy
199 comprised three levels: elements, strategies, and active ingredients. We defined the elements as either
200 specific or non-specific. Nonspecific elements are fundamental engagement strategies (e.g., showing
201 empathy) and are essential for building an effective client-therapist alliance. Specific elements are
202 unique to a particular theoretical orientation underpinned by behavioural, cognitive, interpersonal, and
203 emotional domains. This categorization is recommended by Singla et al. and widely adopted by the
204 stakeholders (Rahman et al., 2018; Waqas et al., 2022b). All these elements and active ingredients

205 have been defined in the World Health Organization's guidelines for preventing and treating perinatal
206 depression and anxiety (Rahman et al., 2018) and presented here for review. The finalized hierarchy
207 of active ingredients comprised 58 most utilized behaviour change techniques and treatment elements
208 (Supplementary Table 3 and 4). Using the above frameworks, we could also harmonize and
209 standardize strategies utilized across different disciplines and theories. For example, "thought
210 records" in cognitive-behavioural therapy were considered similar to "mood ratings" in interpersonal
211 psychotherapy (England et al., 2015).

212 This phase was conducted by three experts trained in clinical psychology and psychiatry at
213 postgraduate levels. The reviewers evaluated the content of the interventions as detailed in the trial
214 papers and associated manuals (if available) to identify commonly utilized approaches.

215

216 **1.2.6. Risk of bias**

217 The risk of bias among RCTs was assessed using the Cochrane tool for risk of bias assessments
218 (Higgins et al., 2019). It was assessed across five domains, including the method for random sequence
219 generation, allocation concealment, blinding of outcome assessment, attrition bias, and selective
220 reporting. We did not rate risk across blinding of participants and personnel domain as it is
221 challenging to maintain during trials of psychotherapies.

222 **1.2.7. Data analysis**

223 We conducted a meta-analysis for depressive symptoms according to psychometric scales and the rate
224 of perinatal depressive disorders (ICD/DSM criteria) assessed after intervention. Findings on
225 secondary outcomes were only synthesized narratively. For continuous outcomes about depressive
226 symptoms severity on psychometric scales, we extracted the mean (SD) and sample size of
227 intervention and control groups. For binary outcomes, we extracted both groups' number of events and
228 sample sizes. In case scores on psychometric scales were presented as binary outcomes in studies, we
229 converted them to standardized mean differences using the following formula: $SMD = \sqrt{3} / \pi \ln OR$
230 (Higgins et al., 2019).

231 We expected a high clinical heterogeneity in the eligible studies due to varied approaches for
232 assessment of clinical outcomes, theoretical underpinnings of included therapies, and population
233 studies. Therefore, we utilized random effects (Der Simonian & Laird method) to pool data across the
234 studies. Study level and pooled effect sizes were visualized as a forest plot. Sensitivity analyses were
235 conducted to adjust meta-analytical estimates for outliers. Publication bias in the study was assessed
236 statistically using Egger's regression and visualized as Begg's funnel plot (Thornton and Lee, 2000).
237 To identify moderators of effect sizes, we conducted subgroup analyses for study, intervention, and
238 patient-level variables if reported in more than four studies (Borenstein et al., 2021). Meta-regression
239 was done to assess the association of quantitative variables with effect size. To ensure optimum

240 power, meta-regression was only performed when continuous variables were reported in at least ten
241 studies. (Borenstein et al., 2021)

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245 **1.3. Results**

246 **1.3.1. Screening process**

247 The electronic database searches yielded 515 titles and abstracts, out of which 116 duplicate records
248 were removed using Endnote. Out of 399 titles and abstracts, 323 records were excluded after
249 assessing their titles and abstracts against the eligibility criteria for this review. Finally, full texts of 76
250 studies were appraised, out of which 34 were excluded. A total of 42 studies were eligible to be
251 included in the review. The main reasons for exclusion were non-RCT/cRCT study design (n=30),
252 intervention not for PND (n=2), and short forms of publication (n=2). Fourteen studies were included
253 after the manual screening of bibliographies of included studies and consultations with experts (Figure
254 1).

255 Among these 56 studies, there were 59 interventions. Among the included studies, a high proportion
256 of the interventions were delivered individually (n=24), followed by group (n=25) and electronic
257 (n=10) delivery format. These interventions were tested among participants with a mean age of 28.48
258 years (\bar{x} =28.48, SD= 2.99), married (\bar{x} =66.8%, SD= 31.95), and (\bar{x} =48.26%, SD= 18.03). Among the participants
259 in included studies, around 41% reported low-income levels (SD= 22.32) and poor education (\bar{x} =
260 35.25, SD= 23.69).

261

262 **1.3.2. Quality of trials**

263 These interventions were tested in generally high-quality trials, where random sequence generated
264 was rated at low risk of bias among 41 studies, allocation concealment (n=29), blinding of outcomes
265 assessment (n=26), attrition bias (n=35), and selective reporting (n=56). The risk of bias was unclear
266 for allocation concealment in 27 studies, blinding of outcome assessment (n=27), attrition bias (n=13),
267 and random sequence generation (n=10) (Figure 2).

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269

270 **1.3.3. Interventions delivered to individuals**

271 Among these interventions (Supplementary Table 5), nine were delivered during the antenatal period
272 (Ammerman et al., 2013; Burns et al., 2013; Cho et al., 2008; Dimidjian et al., 2014, 2016; Hayden et
273 al., 2012; Nejad et al., 2021; Silverstein et al., 2011; Yazdanimehr et al., 2016), followed by postnatal
274 (n=8) (Chabrol et al., 2002; Cooper et al., 2003; Hou et al., 2014; Kordi et al., 2018; Morrell et al.,

275 2009; Ngai et al., 2015; Van Horne et al., 2021) and both periods (n=7) (McKee et al., 2006; O'Mahen
276 et al., 2013a; Prendergast J, 2001; Rahman et al., 2018; Rahman et al., 2008; Sikander et al., 2019b;
277 Tandon et al., 2018; Trevillion, 2014). Eleven interventions were delivered in communities, especially
278 through home visits (Ammerman et al., 2013; Burns et al., 2013; Chabrol et al., 2002; Cooper et al.,
279 2003; Morrell et al., 2009; Prendergast J, 2001; Rahman et al., 2008; Sikander et al., 2019a; Tandon et
280 al., 2018; Van Horne et al., 2021), three in multiple settings (Dimidjian et al., 2017; McKee et al.,
281 2006; Silverstein et al., 2011), while the rest were delivered in healthcare settings (clinic or hospital)
282 (Cho et al., 2008; Dimidjian et al., 2016; Hayden et al., 2012; Hou et al., 2014; Kordi et al., 2018;
283 Nejad et al., 2021; Ngai et al., 2015; O'Mahen et al., 2013a; Trevillion, 2014; Yazdanimehr et al.,
284 2016). A higher proportion of studies utilized EPDS for outcome assessment (n=12), followed by BDI
285 (n=6), HDRS (n=2), PHQ-9 (n=2), QIDS and DASS-21 (n=2).

286 A total of 18 interventions were tested for PND treatment and underpinned by CBT (n=16). Three
287 trials tested PST (Kordi et al., 2018; Silverstein et al., 2011; Van Horne et al., 2021), mindfulness-
288 based stress reduction or cognitive therapy (n=3) (Dimidjian et al., 2016; Nejad et al., 2021;
289 Yazdanimehr et al., 2016), and BA therapy (n=1) (Dimidjian et al., 2017). These interventions were
290 delivered by either specialists (n= 14), non-specialists (n=8), or multidisciplinary teams (n=2).
291 Delivery agents reported diverse disciplinary backgrounds and experience in the delivery of care.
292 Non-specialists ranged from peers (Sikander et al., 2019a), health visitors (Morrell et al., 2009;
293 Tandon et al., 2018), and allied health professionals such as lady health workers (Rahman et al.,
294 2008), midwives (Ngai et al., 2015), early childhood nurses (Prendergast J, 2001), and social workers
295 (Ammerman et al., 2013; Hayden et al., 2012; McKee et al., 2006; Van Horne et al., 2021) and
296 graduate students in social work, public health, and medical sciences (Silverstein et al., 2011). While
297 delivery agents specializing in mental health included practising clinical psychologists, graduate
298 students, recent graduates (Burns et al., 2013; Chabrol et al., 2002; Cho et al., 2008), counsellors, and
299 well-being practitioners (Hou et al., 2014; Trevillion, 2014). Half of these interventions (n=12) were
300 integrated into healthcare settings (Ammerman et al., 2013; Dimidjian et al., 2016; Dimidjian et al.,
301 2017; Hou et al., 2014; Morrell et al., 2009; Ngai et al., 2015; Prendergast J, 2001; Rahman et al.,
302 2008; Sikander et al., 2019a; Tandon et al., 2018; Trevillion, 2014; Van Horne et al., 2021).

303 The number of sessions ranged from one for prevention intervention by Chabrol et al. (Chabrol et al.,
304 2002) to sixteen for treatment (Thinking Healthy Programme) of PND (Rahman et al., 2008). Among
305 non-specific interventions, most frequently utilized non-specific active ingredients were active
306 listening (n=10), empathy (n=9), collaboration (n=9) and inciting social support (n=9) and
307 normalization (n=7). Assigning homework (n=8) and goal setting (n=8) were most frequently utilized
308 in-session techniques.

309 Among specific ingredients, interpersonal strategies were frequently utilized, including identifying
310 and eliciting social support (n=14), communication skills (n=11), and identifying affect (n=10).
311 Among behavioural strategies, problem-solving (n=16), relaxation (n=7), emotional regulation and
312 stress management, and decision making (n=5 each) were frequently utilized. Essential cognitive
313 strategies were identifying thoughts and behaviours and their links (n=19), cognitive restructuring
314 (n=16), self-awareness (n=8), and mood monitoring (n=7). Caregiver coping (n=8), parent-child
315 interaction (n=6), and psychoeducation regarding birth procedures or specific health areas of children
316 (n=6) were also important (Supplementary Figures 1 to 3)

317 **1.3.4. Intervention delivered in groups**

318 Among these 25 interventions (Supplementary Table 6), 14 were delivered antenatally
319 (Austin et al., 2008; Bittner et al., 2014; Brugha et al., 2000; Futterman et al., 2010; Jesse et
320 al., 2015; Kaaya et al., 2013; Khamseh et al., 2019; Kozinszky et al., 2012; Lara et al., 2010;
321 Le et al., 2011; Leung et al., 2013; Van Ravesteyn et al., 2018; Zemestani and Fazeli Nikoo,
322 2019), postnatally (n=7) (Christine Puckering, 2010; Graciela Rojas, 2007; Hagan et al.,
323 2004; Leung SS, 2016; Mao et al., 2012; Milgrom et al., 2005; Van Lieshout et al., 2022),
324 and four during both periods (Muñoz et al., 2007; Ngai et al., 2019; Tandon et al., 2014).
325 Only three of these interventions were conducted in communities (Muñoz et al., 2007;
326 Tandon et al., 2014; Van Lieshout et al., 2022), while the rest were conducted in healthcare
327 settings. EPDS was the most frequently utilized scale for outcome assessment, followed by
328 BDI I/II (n=5). Seven interventions were delivered by specialists, 14 by non-specialists, and
329 four by multidisciplinary teams. Delivery agents were heterogeneous in terms of disciplines
330 and experience and included counselling or clinical psychologists, academics and doctoral
331 students in psychology, nurses, midwives, doctors, obstetricians, social workers, occupational
332 therapists, art therapists, infant mental health specialists, and peers. Thirteen of these
333 interventions were integrated into healthcare systems, while the rest were delivered as
334 standalone.

335 A total of 13 interventions were tested for treatment and 12 for prevention of PND. Twenty
336 trials tested classical CBT interventions, PST (n=2), psychoeducation (n=2) and MCBT
337 (n=1). The sessions ranged from one (Ngai et al., 2019) to 14 (Christine Puckering, 2010).
338 Among group therapies, the most frequently utilized non-specific ingredients were inciting
339 social support (n=12), normalization (n=9), and involvement of significant other (n=6). Most
340 frequently employed in-session techniques were assigning homework (n=11), goal setting
341 (n=13), and interpersonal focus (n=9). Among interpersonal strategies, the most frequently
342 utilized ingredients were identifying affect (n=15), identifying, and eliciting social support
343 (n=13), and communication skills (n=11). Problem solving (n=18), relaxation (n=16), stress
344 management (n=13) were most frequently utilized behavioural ingredients. Identifying
345 thoughts, behaviours, and their links (n=18), cognitive restructuring (n=13), and mood
346 monitoring (n=6) were important cognitive ingredients. Caregiver coping skills (n=8) and
347 parent-child interaction coaching (n=6) were imparted in a small proportion of trials
348 (Supplementary Figures 4 to 6).

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1.3.5. Interventions delivered online

351

352 Seven of these interventions (Supplementary Table 7) were tested during postpartum (Fonseca et al.,
353 2020; Jannati et al., 2020; Loughnan et al., 2019a; Milgrom et al., 2016; O'Mahen et al., 2013b; Van
354 Lieshout et al., 2021; Wozney et al., 2017) and three during the antenatal period (Duffecy et al., 2019;
355 Forsell et al., 2017; Loughnan et al., 2019b). Two of these interventions were for the prevention of
356 perinatal depression (Duffecy et al., 2019; Fonseca et al., 2020), while the rest were treatment
357 interventions. All interventions were designed to be used by individuals, except Duffecy et al. and
358 Van Lieshout et al. who delivered to groups of participants (Duffecy et al., 2019; Van Lieshout et al.,
359 2021). Only two of these interventions were guided either by specialist mental health professionals
360 (Van Lieshout et al., 2021) or non-specialists (Wozney et al., 2017). The number of sessions of
361 interventions ranged from one (Van Lieshout et al., 2021) to 16 (Duffecy et al., 2019). Only one
362 intervention was integrated into healthcare settings (Forsell et al., 2017).

363 All interventions were based on CBT except Fonseca et al. and O'Mahen et al., who tested CBT-ACT
364 and BA-based interventions (Fonseca et al., 2020; O'Mahen et al., 2013b). Among these
365 interventions, inciting social support (n=6) was the most frequently utilized non-specific ingredient.
366 Identifying affect (n=9), identifying and eliciting social support (n=8), and communication skills
367 training (n=7) were important interpersonal strategies. Problem-solving (n=7), relaxation (n=7), and
368 self-monitoring were important behavioural approaches. Among cognitive approaches, identifying
369 thoughts (n=10), cognitive restructuring (n=8), and mood monitoring (n=7) were important elements.
370 Assigning homework (n=6) was frequently employed in-session technique. Caregiver coping and
371 parent-child interaction coaching were utilized in four interventions.

372 None of the interventions employed reinforcement-oriented active ingredients. Four interventions
373 included information on caregiver coping skills (Duffecy et al., 2019; Fonseca et al., 2020; Milgrom
374 et al., 2016; O'Mahen et al., 2013b) and four included parent-child interaction coaching (Duffecy et
375 al., 2019; Milgrom et al., 2016; O'Mahen et al., 2013b; Wozney et al., 2017). Psychoeducation, either
376 on birth procedures, nutrition, breastfeeding, or sexual behaviours was provided in only two
377 interventions (Duffecy et al., 2019; Milgrom et al., 2016). Nutrition and substance use-related
378 counselling were each provided in one study (Duffecy et al., 2019; Wozney et al., 2017). Table 4-6
379 present the characteristics of studies included in this section. Supplementary figures 7 to 9 present
380 active ingredients utilized in online interventions

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382 1.3.6. Meta-Analysis: Effectiveness

383 CBT based interventions yielded a strong effect size (SMD= -0.74, 95% CI: -0.91 to -0.56, n= 9,722)
384 in alleviating depressive symptoms. There was evidence of substantial heterogeneity in effect sizes
385 across studies ($I^2= 92.65\%$, $p < 0.001$, $Q= 775.03$). Sensitivity analysis did not reveal any substantial
386 changes in effect size after removing outliers. There was substantial publication bias, as evidenced by
387 the funnel plot (Supplementary Figure 10) and Egger's regression statistic ($p=0.009$). Duval &
388 Tweedie's trim and fill method adjusted pooled effect size for publication bias. After trimming 13
389 studies to the left of the mean, the adjusted SMD was -0.95 (95% CI: -1.14 to -0.76).
390 Forest plots were developed separately according to the mode of delivery of interventions.
391 Interventions delivered electronically (n=9) yielded strong effect sizes (SMD= -1.12, 95% CI: -1.80 to
392 -0.63, n=1218) (Figure 3). There was substantial evidence of heterogeneity across studies ($I^2=$
393 93.99% , $p < 0.001$, $Q= 133.12$). There was no evidence of publication bias (Egger's regression
394 $p=0.65$). Intervention delivered to individuals (Figure 4) also yielded strong effect sizes in favor of
395 intervention group (SMD= -0.63, 95% CI: -0.81 to -0.44, n= 3589). There was evidence of significant
396 heterogeneity across the studies ($I^2= 80.99\%$, $p<0.001$, $Q=121.02$). There was evidence for significant
397 publication bias (Egger's regression $P=0.06$), which after adjustment led to a higher effect size
398 (SMD= -0.75, 95% CI: -0.94 to -0.55). Interventions delivered among groups (Figure 5) also yielded
399 strong effect sizes in favour of the intervention group (SMD=-0.67, 95% CI: -0.96 to -0.38, n=4915).
400 Statistical heterogeneity was substantial ($I^2= 94.59\%$, $p<0.001$, $Q=443.90$). There was some evidence
401 of publication bias (Egger's regression $p=0.10$), with the trim & fill method yielding a higher adjusted
402 effect size (SMD= -1.00, 95% CI: -1.33 to -0.67). Sensitivity analysis did not reveal any substantial
403 changes in effect size after removing outliers in any of the above analyses.

404

405 1.3.7. Moderator analyses: Intervention level characteristics

406 Moderator analyses for intervention level characteristics yielded several important insights
407 (Supplementary Table 8). Interventions for treatment (SMD= -0.94, 95% CI: -1.15 to -0.73) of
408 perinatal depressive symptoms yielded significantly higher effect sizes than preventive ones (SMD= -
409 0.36, 95% CI: -0.65 to -0.07). Interventions offered as tested as stand-alone programmes (SMD= -
410 1.01, 95% CI: -1.24 to -0.79) performed better than those integrated in healthcare settings (SMD= -
411 0.38, 95% CI: -0.63 to -0.14).
412 Effect sizes did not differ according to the delivery format, where no differences were observed
413 between interventions delivered either through electronic means, face-to-face in groups, or
414 individually ($Q=4.76$, $p=0.09$). Delivery agents with varying disciplinary backgrounds:
415 multidisciplinary teams, non-specialists, online interventions, and those delivered by specialists, were

416 effective. Although interventions delivered electronically and through specialists had slightly higher
417 effect sizes, this did not reach statistical significance ($Q=4.05$, $p=0.26$).

418 **1.3.8. Moderator analysis: Participant-level characteristics**

419 Higher effect sizes were associated with interventions recruiting perinatal women with higher age ($b=$
420 -0.07 , $SE= 0.01$, $p<0.001$) (Supplementary Table 9). While interventions with a higher proportion of
421 perinatal women belonging to minorities, low-income levels, reporting poorer education, and
422 recurrent episodes of depression yielded smaller effect sizes. The proportion of married or
423 primiparous women in trials was not associated with effect sizes yielded by included interventions.
424 Interventions delivered during postnatal had a higher effect size than those delivered during the
425 antenatal period, or during both periods; however, this was statistically non-significant.

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428 **1.3.9. Moderator analysis: Active ingredients**

429 When considering the theoretical underpinnings of included interventions, dose of intervention was
430 inversely associated with effect sizes ($b= 0.016$, $p<0.01$). Most of the trial evidence included in this
431 review tested CBT interventions ($n=42$), which yielded strong effect sizes ($SMD= -0.70$, 95% CI: -
432 0.91 to -0.49). PST was tested in five trials and yielded comparable effect sizes (-0.71 , 95% CI: -1.32
433 to -0.11). BA yielded moderate strength effect sizes ($SMD= -0.32$, 95% CI: -1.05 to 0.42). However,
434 evidence about these was inconclusive due to overlapping effect sizes, despite reaching statistical
435 significance.

436 Among intervention ingredients, using more behavioural ingredients in CBT interventions yielded
437 high effect sizes ($b= -0.079$, $p< 0.01$). An inverse trend was noted for interventions including
438 reinforcement-related ingredients ($b= 0.2$, $p<0.01$). Interventions including a higher number of
439 cognitive and interpersonal ingredients, parenting skills, psychoeducation, exercise, in-session
440 techniques, nutrition, and substance use-related counselling did not yield statistical significance
441 (Table 4-9). When individual active ingredients were considered, the presence or absence of
442 interpersonal, cognitive, and behavioural ingredients did not alter effect sizes. Interventions utilizing
443 *identifying affect* and *self-awareness* strategies yielded larger effect sizes than their counterparts
444 (Table 4-10).

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455 **1.4. Discussion**

456 The present systematic review presents up-to-date evidence regarding the effectiveness of CBT for
457 PND. It delineates several interesting insights for optimizing CBT-based interventions for PND. We
458 found that CBT interventions, including third-wave cognitive therapies, are highly effective in
459 preventing and treating PND. CBT can be delivered effectively to individuals and in groups or online
460 web or app-based software. The delivery of CBT can also be tailored according to the resources
461 available, for instance, by employing specialists or non-specialists' delivery agents. Interventions
462 integrated into healthcare settings and utilizing the available infrastructure may be less effective than
463 stand-alone programmes. Perinatal women experiencing adverse events and health inequalities report
464 smaller effect sizes when treated with CBT. The effectiveness of CBT also depends on several
465 intervention-level characteristics.

466 CBT interventions yielded strong effect sizes for treatment and moderate strength effect sizes for
467 preventing PND. These findings are corroborated by previous meta-analyses, which have yielded
468 similar effect sizes for CBT interventions for PND (Rahman et al., 2013; Rahman et al., 2018; Sockol,
469 2015; Waqas et al., 2022b). CBT interventions are also recommended by the US Preventive Services
470 Taskforce and the WHO (Curry et al., 2019; Rahman et al., 2018). Previous evidence has shown that
471 CBT-based interventions are effective for PND and generally acceptable to stakeholders, delivery
472 agents, and end-consumers (Morrell et al., 2009; Rahman et al., 2018). CBT interventions can be
473 tailored to settings depending on the availability of resources. Both the NICE and the WHO
474 recommend a stepped-care approach to treating PND (Delgado et al., 2022; National Institute for
475 Health and Care Excellence, 2020; Rahman et al., 2018), ranging from self-help psychoeducational
476 materials to low-intensity and high-intensity psychotherapies.

477 There has been an increasing focus on preventing PND. Recently, based on evidence from high
478 income countries, the USPSTF has recommended the use of CBT and counselling interventions for
479 PND (Curry et al., 2019). While the WHO have recommended that all perinatal women should be
480 offered psychosocial interventions to develop coping, stress management and social skills (Guidelines
481 Review Committee, 2022). Whereas women at high risk of developing PND should be offered
482 psychological interventions such as CBT and interpersonal therapy. The provision of these
483 interventions should be allowed as per availability of resources and women's preference. Our
484 systematic review corroborates this evidence and presents CB-based approaches (both specialist and
485 non-specialist delivered) as effective in preventing depression during the perinatal period. We also
486 found that CB based approaches yield good effect sizes across all modes of delivery (electronic,

487 individual or group). This flexibility in delivery increases the utility of CB-based approaches in
488 different settings.

489 While reviewing the intervention level characteristics, several valuable insights were revealed. Firstly,
490 these interventions work when delivered antenatally or postnatally, with little difference in effect
491 sizes. This finding does not agree with our previous systematic review on preventive interventions
492 where a higher effect size was demonstrated for interventions starting early during the antenatal
493 period (Waqas et al., 2022b). This finding also contradicts Sockol's meta-analysis of 26 treatment
494 interventions, where more considerable reductions were noted for interventions initiated during the
495 postpartum period or across the perinatal period (Sockol, 2015). Secondly, CBT interventions
496 delivered either to individuals or groups or online yield similar strength of effect sizes, also
497 corroborated by previous systematic reviews (Sockol, 2015).

498 Interventions integrated into healthcare settings and utilizing the available infrastructure may be less
499 effective than stand-alone programmes. This interesting insight emphasizes the importance of
500 effective implementation measures to ensure adequate implementation, supervision, and competency
501 measures (Ahmad et al., 2020; Zafar et al., 2016). A critical case study in this context is that of the
502 Thinking Healthy Programme developed by one of the co-authors (Rahman et al., 2008). It is a highly
503 effective low-intensity CBT-based intervention that has been endorsed by the WHO for the treatment
504 of PND (World Health Organization, 2015). Integrated into the primary healthcare system, it
505 employed lady health workers as the delivery agents (Rahman et al., 2008). In the following years, a
506 trial was run to test the effectiveness of THP delivered by peers with lived experience of PND
507 (Sikander et al., 2019a). These innovations ensured that the THP remained cost-effective and
508 acceptable to the stakeholders. In addition to innovations in delivery, newer approaches in enhanced
509 supervision, competency assessments, and training at a large scale were also tested to ensure seamless
510 implementation of the THP in communities (Ahmad et al., 2020; Zafar et al., 2016).

511 While reviewing the active ingredients of included interventions, several insights emerged. In
512 comparison with the face-to-face delivered CBT programmes, the ingredient of empathy was missing
513 in electronically delivered interventions. However, this collection of interventions yielded pooled
514 effect sizes comparable to the interventions delivered face to face. This is an important finding as
515 empathy is the foundation for an effective therapeutic patient alliance (Morrell et al., 2009).
516 Therefore, there is a need to open further the black box of the causal mechanisms at play that drive the
517 effectiveness of electronic interventions without the opportunity to build an empathy-based
518 therapeutic relationship. Another interesting finding was that longer interventions were associated
519 with a decrease in effect size. This association may be driven by burnout among either the patient or
520 therapist. We also investigated the dosage density of therapeutic strategies and their association with
521 effect sizes. Only one significant association emerged, where an increase in behavioural ingredients in

522 a therapeutic programme led to an increase in effect size. This strengthens the previous notion that
523 (Kahl et al., 2012) efficacy of the cognitive therapy depends critically on the behavioural activation
524 component rather than its content-oriented cognitive approaches. However, this is inconclusive and
525 warrants further investigation, especially for PND, due to the lack of RCTs, for instance, those
526 comparing efficacy of BA with classical CBT therapies. This is indeed an important area for further
527 research.

528 Lastly, we found that younger perinatal women reported poor education and belonging to lower
529 economic, and minority ethnic classes reported a lower reduction in PND symptoms. This finding is
530 significant and highlights the importance of contextual factors affecting community health and
531 community-oriented policies and initiatives. Multidisciplinary approaches, such as mass education
532 and poverty alleviation initiatives, are required to tackle this issue. In this regard, Banerjee and
533 colleagues' Nobel prize-winning multifaceted program rooted in developmental economics is a
534 crucial case study (Banerjee et al., 2015). Such initiatives are necessary to curb the effects of societal
535 adversities impeding the efficacy of psychological treatments. This has been shown in a huge body of
536 literature demonstrating the complexity of perinatal depression among women facing adversities
537 (Ashman et al., 2008; Bao et al., 2016; Chae et al., 2020).

538 Meta-regression analyses revealed weakly inverse association between proportion of women with
539 history of mental health problems and intervention effect size. There is unequivocal evidence that
540 complex presentations of PND (increased severity, relapsing and recurrent) is associated with poorer
541 treatment response (Ahmed Waqas, 2022). A recent systematic review of observational studies
542 demonstrates that perinatal women with complex and more severe forms of PND report more
543 psychosocial adversities (Ahmed Waqas, 2022). Moreover, if left untreated, such PND symptoms
544 contribute to intergenerational transfer of inequities; whereby children born to women with complex
545 PND report poorer academic, mental, and physical health outcomes. Despite a plethora of
546 observational research evidence, investigators have not yet focused on development of bespoke
547 interventions for either preventing relapse or treating recurrent episodes of perinatal depressive
548 disorder. This is also true for pharmacological trials where little evidence is present for prevention of
549 relapse of depression during the perinatal period (Molyneaux et al., 2018). Evidence is emerging
550 however, where a recent two arm, parallel design RCT tested a parenting video-feedback therapy
551 intervention added to CBT in treatment of persistent postpartum depression (Stein et al., 2018). The
552 NICE recommends high intensity psychotherapies or antidepressants for women at a high risk of
553 relapse (National Institute for Health and Care Excellence, 2020).

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555 **1.5. Strengths and limitations**

556 This systematic review has several strengths. Firstly, this systematic review and meta-regression
557 analysis provide a comprehensive and up-to-date estimate of the effectiveness of CBT. It provides
558 reliable estimates of the effectiveness of CBT delivered by specialist and non-specialist workforces.
559 Furthermore, this review utilizes a large pool of RCTs. This allowed us to investigate the moderating
560 effects of intervention and patient-level characteristics in detail. We also present novel findings on the
561 active ingredients of CB-based approaches by leveraging the distillation and matching framework.
562 Effects of dose density and active ingredients comprising CB interventions yielded valuable insights.

563 However, despite its strengths, this review has several limitations. Firstly, conducting distillation and
564 matching framework exercises to map active ingredients of therapies is complex. The accuracy of this
565 endeavour depends on the information regarding the content of interventions provided in primary
566 studies. Interventions such as the THP (developed by the co- author AR) (Rahman et al., 2008)
567 provided details and content of the intervention in open-access manuals (World Health Organization,
568 2015). This approach is important and aids in future evidence synthesis studies and reproducibility
569 and adaptability in different cultures. These analyses are also limited by the observational nature of
570 meta-regression analyses used to study moderators of CB interventions. Therefore, this evidence
571 should be interpreted with caution.

572 The present meta-analysis utilized subgroup analyses to compare effectiveness of CB-based
573 approaches utilizing specific active ingredients. These analyses can be improved by using meta-
574 analytic structural equation modeling approaches (Harrer et al., 2021). The use of these complex
575 methods can aid in our understanding of causal mediation mechanisms in psychotherapies.

576 Another key limitation inherent to using meta-regression analyses is the use of across-trial data and
577 aggregated values for the participant and intervention-level characteristics for analyses. Such analyses
578 are limited due to inherent aggregation bias and may not reflect actual treatment-covariate interactions
579 (Huh et al., 2019; Kelley and Kelley, 2012). These limitations, in theory, can be offset by using two-
580 stage Individual Participant Data Meta-analysis (IPDMA) approaches which use within-trial
581 information to estimate treatment-covariation interactions (Kelley and Kelley, 2012). IPDMAs
582 involving a large pool of datasets are time and resource intensive; however, we encourage researchers
583 to utilize these approaches in the future. A recent example of this approach is Furukawa and
584 colleagues' work (Furukawa et al., 2021), which presents a web application to estimate relative
585 efficacies, and additive and synergistic effects yielded through combinations of specific and
586 nonspecific components in internet-delivered CBT interventions in the context of patient-level
587 variables. Future meta-investigations should also consider utilizing realist evaluation using both
588 quantitative and qualitative approaches to distill important insights on CBT for PND.

589 Furthermore, the subgroup and meta-regression analyses in this systematic review were run for a
590 limited number of participant-level and intervention-level factors. Many other factors such as
591 experience of intimate partner violence (Keynejad et al., 2020), family structure, social support
592 networks and chronicity of PND are important moderators and should be considered in future reviews
593 (Waqas et al., 2022a). Moreover, researchers should consider collecting detailed data on moderators
594 of treatment for perinatal depression in their future trials. We focused on CB-based approaches to
595 meta-analyze a homogeneous set of interventions in the present systematic review. Other
596 psychotherapeutic modalities should be reviewed in future meta-analyses, keeping in mind the clinical
597 and statistical heterogeneity often encountered in psychotherapy literature.

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600 **1.6. Conclusion**

601 Cognitive behavioural therapies are highly effective in reducing the severity of PND. Most of the trial
602 evidence included in this review tested classical CBT approaches. And there is limited evidence for
603 third-wave CBT for PND. CBT is effective when delivered across individual, group, and electronic
604 platforms and thus can be tailored according to the financial and human resources available. Longer
605 duration CBT interventions may not necessarily be more effective than shorter ones. Furthermore,
606 CBT-based interventions should consider including various behavioural ingredients to maximize
607 intervention benefits.

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611 **Author Contribution Statement**

612 This systematic review and meta-analysis was conceived by AW and AR. AW and AR wrote the
613 protocol and registered it in PROSPERO. AW & PA searched the databases and performed screening
614 of titles and abstracts and full texts for eligibility. AW and SN extracted data on characteristics of
615 intervention and population. AW, PA and SWZ extracted data pertaining to components of
616 interventions. AW and SN extracted quantitative data. AW conducted the meta-analysis. AW wrote
617 the initial draft of the manuscript. All authors critically reviewed the manuscript and approved it for
618 submission.

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621 **Conflict of Interest Statement**

622 The authors have no conflict of interest to report.

623 **Ethics statement**

624 Not applicable.

625 **Data Availability Statement**

626 All data associated with this manuscript are available as supplementary files.

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629 **References**

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978 **Figure 1: PRISMA flowchart demonstrating the process of inclusion of studies**

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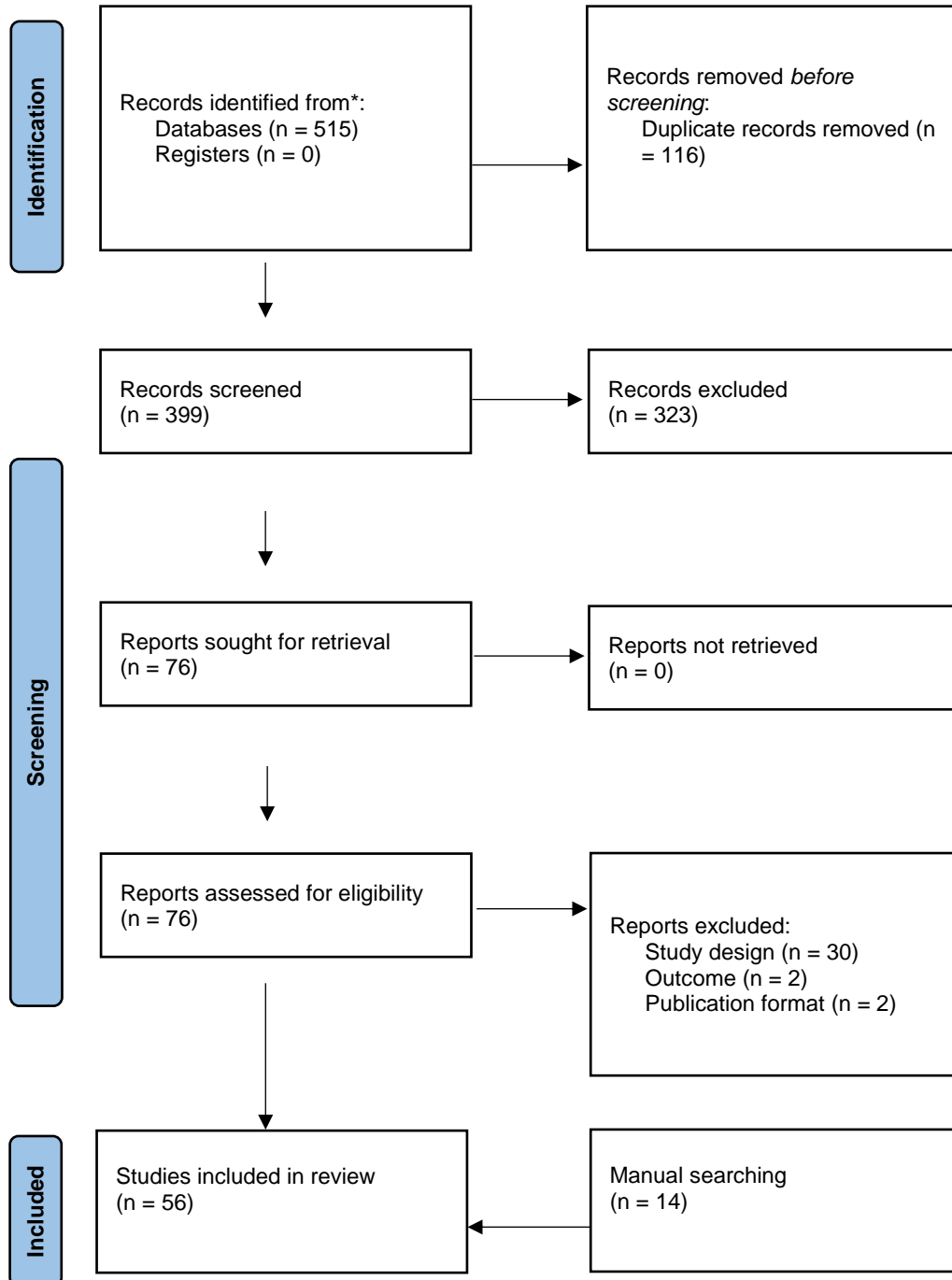
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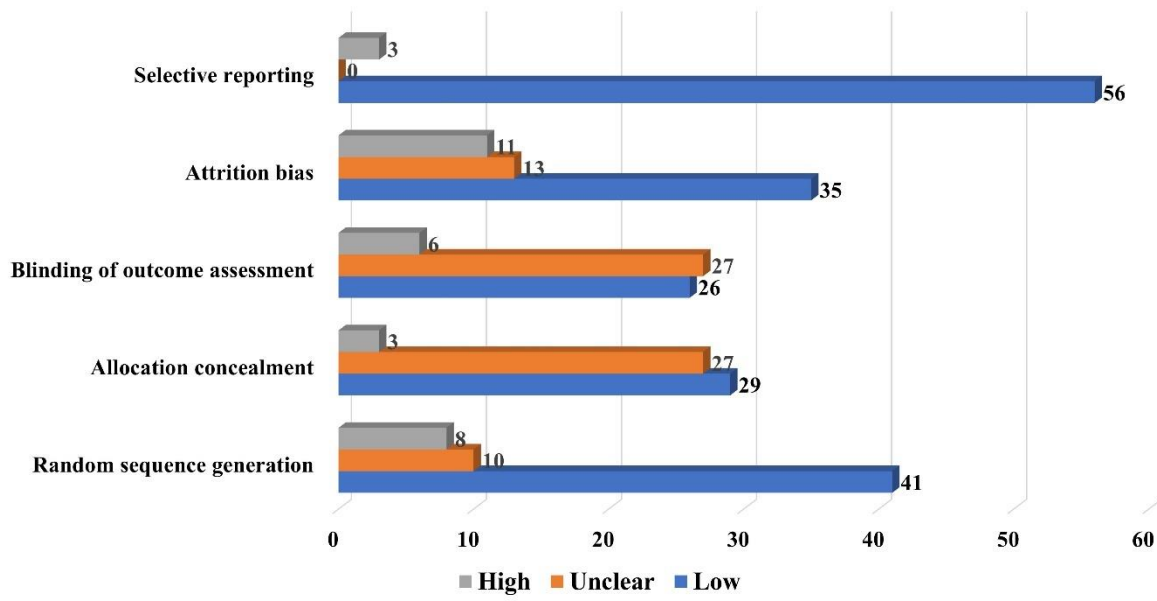
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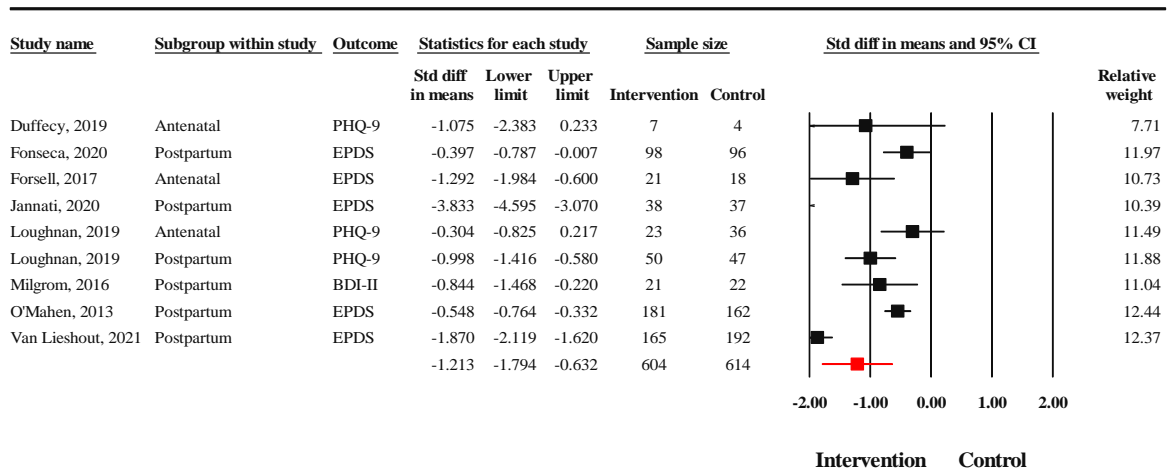
1014 **Figure 2: Risk of bias in included studies**



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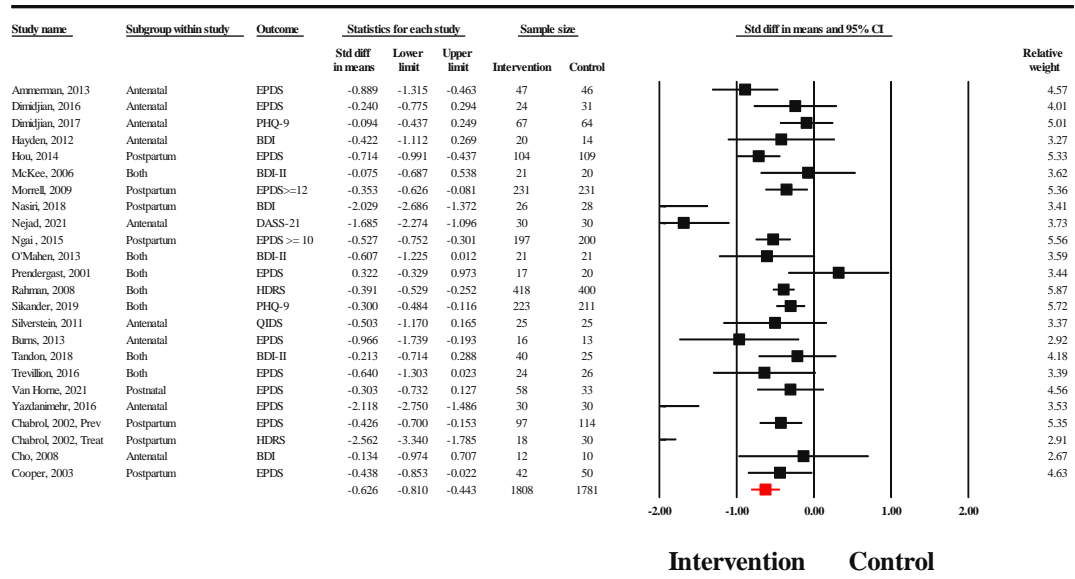
1017 Figure 3: Forest plot visualizing effect sizes for interventions delivered online (n=9)



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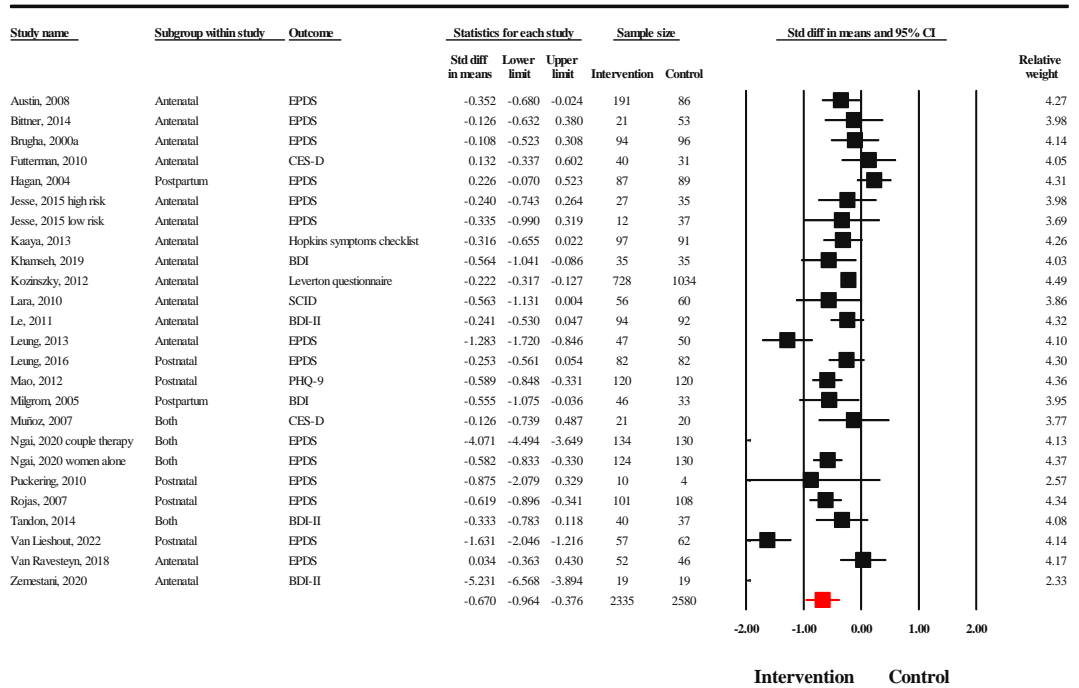
1020 Figure 4: Forest plot visualizing effect sizes for interventions delivered to individuals (n=24)



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1023 **Figure 5: Forest plot visualizing effect sizes for interventions delivered to groups (n=25)**



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