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META-ANALYSIS

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Postpartum hemorrhage and postpartum depression: A systematic review and meta-analysis of observational studies

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Abstract

Objective: To assess the postpartum depression (PPD) risk in women with postpartum hemorrhage (PPH) and moderators.

Methods: We identified observational studies of PPD rates in women with versus without PPH in Embase/Medline/PsychInfo/Cinhail in 09/2022. Study quality was evaluated using the Newcastle-Ottawa-Scale. Our primary outcome was the odds ratio (OR, 95% confidence intervals [95%CI]) of PPD in women with versus without PPH. Meta-regression analyses included the effects of age, body mass index, marital status, education, history of depression/anxiety, pre-eclampsia, antenatal anemia and C-section; subgroup analyses were based on PPH and PPD assessment methods, samples with versus without history of depression/anxiety, from low-/middle- versus high-income countries. We performed sensitivity analyses after excluding poor-quality studies, cross-sectional studies and sequentially each study.

Results: One, five and three studies were rated as good-, fair- and poor-quality respectively. In nine studies (k = 10 cohorts, n = 934,432), women with PPH were at increased PPD risk compared to women without PPH (OR = 1.28, 95% CI = 1.13 to 1.44, $p < 0.001$), with substantial heterogeneity ($I^2 = 98.9\%$). Higher PPH-related PPD ORs were estimated in samples with versus without history of depression/anxiety or antidepressant exposure (OR = 1.37, 95% CI = 1.18 to 1.60, k = 6, n = 55,212, versus 1.06, 95%CI = 1.04 to 1.09, k = 3, n = 879,220, $p < 0.001$) and in cohorts from low-/middle- versus high-income countries (OR = 1.49, 95%CI = 1.37 to 1.61, k = 4, n = 9197, versus 1.13, 95% CI = 1.04 to 1.23, k = 6, n = 925,235, $p < 0.001$). After excluding low-quality studies the PPD OR dropped (1.14, 95%CI = 1.02 to 1.29, k = 6, n = 929,671, $p = 0.02$).

Conclusions: Women with PPH had increased PPD risk amplified by history of depression/anxiety, whereas more data from low-/middle-income countries are required.

KEYWORDS

antidepressants, mood disorders, perinatal mental health, postpartum depression, postpartum hemorrhage

1 | INTRODUCTION

Postpartum hemorrhage (PPH) is between leading causes of obstetric morbidity and mortality worldwide with up to 11% of all maternal deaths being related to PPH.[1] There is an essential variation regarding prevalence/incidence of PPH heavily depending on the criteria used as well as on the mode of delivery, with estimates suggesting that PPH may affect up to approximately one out of 10 birth-giving women.[2,3] Moreover, epidemiological data report a gradually increasing prevalence of PPH during the past decades.[4,5]

Based on the International Classification of Diseases (ICD-10) PPH is defined as a blood loss in excess of 500 mL following vaginal delivery or >1000 mL after a cesarean delivery.[6] Occasionally, defining PPH based on a single blood loss volume cut-off received criticism, as women may respond differently to a specific amount of blood loss.[7] More recent guidelines considered slightly modified criteria such as a cumulative blood loss of ≥1000 mL accompanied by signs or symptoms of hypovolemia, regardless of the mode of delivery.[8] Additionally, the Royal College of Obstetrics and Gynecology classifies PPH as minor for blood loss between 500 and 1000 mL, moderate for 1000–2000 mL and severe >2000 mL.[9] Regarding time frame of blood loss, PPH is considered to primary when it occurs within the first 24 h and secondary between 24 h and up to 12 weeks after birth.[10] There are several widely embraced PPH risk factors including placental complications, macrosomia, maternal obesity and gestational age,[11,12] whereas among causes of PPH uterine atony accounts for around 70% of the cases.[13] Concerning the immediate sequelae of PPH, severe anemia requiring blood transfusion, intravascular coagulopathy, hysterectomy, and death are quite common.[14,15] Late complications may include fertility problems,[16] while there is an emerging body literature linking PPH and postpartum depression (PPD).[17,18]

On the other hand, PPD is characterized by symptoms of major depression occurring after birth[19] affecting a substantial amount of mothers with prevalence rates of PPD ranging between 10% and 25% worldwide.[20] Additionally, PPD has been associated with severe maternal and familiar distress,[21] suicidal risk,[22] as well as impaired development and behavior outcomes of the child.[23]

Although the mechanisms potentially linking PPH and PPD remain poorly understood, PPH and PPD may share some common pathways.[24] For example, the traumatic delivery experience associated with fatigue following severe PPH could be related to prolonged affective symptoms.[24] Moreover, PPH may lead to postpartum anemia, which has been associated with elevated risk of PPD.[19] Further, anemia during pregnancy is a risk factor for both PPH and PPD.[12,19,25] Other joint risk factors for both PPH and PPD that could account for shared mechanisms include obesity and C-section.[12,19,26] Additionally, over the last years there is a vivid debate concerning the role of antidepressant exposure potentially predisposing to PPH, but also being a surrogate of antenatal mental distress.[27] Specifically, sustained antidepressant exposure

Summations

- Women with postpartum hemorrhage (PPH) are at increased risk of postpartum depression (PPD) compared to women without.
- The elevated PPD risk in women with PPH may be amplified by history of depression or anxiety.
- Further research is required to understand the interplay between PPH and history of mental distress in shaping the risk of PPD.

Limitations

- Studies assessing the risk of postpartum depression (PPD) in women with postpartum hemorrhage (PPH) suffered from essential heterogeneity.
- Studies assessing the risk of PPD in women with versus without PPH unfrequently matched for known confounders.
- Further studies need to assess the role of antidepressant exposure within the interplay between PPH and the risk of PPD.

during pregnancy may be associated with increased risk of preeclampsia and postpartum hemorrhage,[27,28] although it is not always simple to disentangle the effects of antidepressants and the depression. Earlier evidence had suggested that exposure to all types of first-line antidepressants is associated with elevated risk of PPH,[29] although it is advised that this risk may be smaller compared to obstetric risk factors of PPH.[30] Ultimately, the antidepressant exposure may be a surrogate of depression or anxiety during pregnancy, which is a well-known risk factor of PPD.[31] Interestingly, two studies excluding women with history of mental illness before birth did not suggest elevated risk for new-onset PPD in women with PPH.[32,33]

Our aim was to conduct a systematic review and meta-analysis of observational studies to assess the association between PPH and the risk of PPD in women as well as potential moderators.

2 | MATERIALS AND METHODS

This study was conducted according to MOOSE (Meta-analyses Of Observational Studies in Epidemiology) guidelines for meta-analyses of observational studies[34] and the protocol was registered in advance with PROSPERO (registration number CRD42022320126). Studies investigating PPD rates in women with versus without PPH were identified by searching Embase and Medline, using the following search strategy: (postpartum hemorrhage [MeSH Terms]) OR AND "depress*" AND (postpar* OR postnat* OR (postpartum depression [MeSH Terms])) by two researchers (GS and CG). Database search was last performed in September 2022 for publications, without language restriction since data inception. References from identified articles were afterwards hand-searched for further studies of interest.

2.1 | Eligibility criteria, information sources, search strategy

2.1.1 | Study selection

Cohort, case-control, and cross-sectional observational studies reporting on PPD rates in women with versus without PPH were included. We did not include studies without comparator group or not stratifying for PPD rates with regard to PPH exposure (or lack of). Selection of eligible studies was independently performed by two researchers (CG and GS). Consensus was reached in all cases, so that no additional person was involved.

2.1.2 | Types of participants

Women with primary or secondary PPH were included. There were no restrictions with regards to diagnostic criteria of PPH.

2.1.3 | Comparator

Women without PPH.

2.1.4 | Types of exposure

Diagnosis of PPH regardless of the assessment method.

2.1.5 | Outcomes

The primary outcome was the odds ratio (OR) for PPD symptoms or diagnosis in women with versus without PPH. Meta-regression analyses assessing the effects of age, body mass index (BMI), percentage single/divorced mothers, maternal education level not higher than high school, history of depression or anxiety, preeclampsia, anemia during pregnancy and cesarean section (C-section) were performed.

2.1.6 | Data extraction

Two authors (GS and CG) extracted data with regard to sample sizes, study design, demographic and clinical characteristics, perinatal complications and assessment methods for PPH and PPD in an independent fashion.

2.1.7 | Quality of studies

The modified versions of the Newcastle-Ottawa scale (NOS) for cross-sectional and cohort studies were used for quality assessment[35]; we removed the item "representativeness of the exposed cohort", that we judged to be related to applicability, and added ascertainment of PPH diagnosis as described elsewhere.[36,37]

2.1.8 | Data synthesis

We applied a random-effects model for our primary outcome, given the potential heterogeneity related to study populations and assessment methods for both exposure and outcome. We summarized results using

ORs and 95% confidence intervals (95%CI) presented in forest plots. For the estimation of heterogeneity variance parameter (τ^2) we used the DerSimonian-Laird estimator.[38] Additionally, we calculated the I-square (I^2) statistic as a measure of the proportion of variability potentially attributed to heterogeneity.[39] Further, the effects of several demographic as well as clinical parameters were assessed in a meta-regression analysis.[40]

Subgroup analyses included samples assessed with different assessment methods for PPH and PPD. Regarding assessment of PPH previous research has demonstrated that ICD-10 coding for PPH has moderately high sensitivity and excellent specificity.[41] Further subgroup analyses were based on the timepoint of PPD assessment as well as groups with versus without previous history of depression or antidepressant exposure; antidepressant exposure may essentially contribute to the risk of PPH.[28] Moreover, we performed a subgroup analysis comparing studies from low- and middle-income countries (LMICs) and non-LMICs. Last, sensitivity analyses excluding low-quality studies, cross-sectional studies and sequentially excluding one study at a time were conducted. To perform analyses we used the `metagen` package in R.[42]

2.1.9 | Assessment of risk of bias

To assess the potential of publication bias we used funnel plots and the Egger's test.[43]

3 | RESULTS

The electronic data base search yielded 90 citations from Medline, 393 from Embase and one from the full-text reviewed articles' reference lists. After removing duplicates, 410 unique studies remained. After exclusion of 377 records based on title and abstract review, 33 articles were full-text screened, leading to rejection of 17 papers due to types of exposure other than PPH, five papers due to outcome other than PPD rates, three papers due to lack of stratified PPD or PPH data in the study groups, three papers due to lack of control group, one comment and one paper due to data overlap. One study was added later on during review process, as authors were provided data from a previous cohort study that had not focused on the role of PPH. Ultimately, nine studies fulfilled all inclusion criteria and were used for data extraction (Figure S1).[17,18,32,33,44–48] An additional search in PsychInfo and Cinhail did not report any further studies of interest.

3.1 | Study characteristics

Of the nine studies including ten cohorts there were five cohort studies, two cross-sectional studies and two case-control studies. The total number of participants was 931,432 including 46,508 women with PPH, the mean age was 30.6 ± 5.5 years, the mean BMI 24.3 ± 6.8 kg/m^2 (Table 1). Two studies matched study groups for both history of depression or anxiety and mode of delivery, four studies matched study groups by history of depression or anxiety, whereas three studies did not match by any of the two variables (Table 1).

3.2 | Risk of bias of included studies

3.2.1 | Quality assessment

The Table S1 summarizes the quality assessment of individual studies, according to the NOS. Of the nine studies, one was rated as high, five as fair and three as poor quality (Table S1). Quality concerns were mainly raised due to lack of matching processes between women with versus without PPH.

3.2.2 | Publication bias

Neither the visual inspection of funnel plots (Figure S2) nor the Egger's test results ($p = 0.23$) revealed any signs of publication bias.

3.3 | Primary outcome

All nine included studies provided data suitable for the primary analysis regarding the risk of developing PPD associated with PPH. Women experiencing PPH were at increased risk of PPD compared to women without PPH, with an OR of 1.28 (95%CI = 1.13 to 1.44, $p = 0.0012$, k = 10, n = 934,432, $p < 0.001$) (Figure 1). Heterogeneity was high ($I^2 = 98.9\%$, $\tau^2 = 0.03$).

3.3.1 | Meta-regression analyses

In our meta-regression analyses higher ORs of PPD were moderated by younger study sample age and history of depression/anxiety (estimated co-efficient −0.11, 95% CI = -0.21 to −0.01, $p = 0.03$ and estimated co-efficient 0.01, 95%CI = 0.002 to 0.01, $p = 0.04$ respectively). We did not observe any effects for BMI (estimated co-efficient −0.06, 95%CI = -0.21 to 0.10, $p = 0.49$), marital status

TABLE 1 Characteristics of included studies (in chronological order).

Study (Country)	Study design	Sample size	PPH	n	n PPD	Matched/comparable for: Mode of delivery	Matched/comparable for: Any psychiatric comorbidities	Age (SD), years	BMI (SD), kg/m^2	Marital status (Single or divorced) [n (%)]	Education level (not higher than high school) [n (%)]	History Depression or anxiety [n (%)]	Pre-eclampsia [n (%)]	Anemia during pregnancy [n (%)]	C-section [n (%)]	Assessment PPD: Time-point (days)	Assessment PPD: Scales	PPH	Quality
Ricbourg et al., 2015[46] (France)	Case-control	40	Yes	20	3	√	√[a]	31.0 (NP)	NP	1 (5.0)	NP	0 (0.00)	NP	NP	7 (35)	30	EPDS	NP	Fair
			No	20	7			30.5 (NP)	NP	1 (5.0)	NP		NP	NP	7 (35)				
Zafar et al., 2015[48] (Malawi)	Cross-sectional	535	Yes	30	NP	x	x	24.3 (5.1)	22.8 (3.1)	NP	NP	71 (1.2)[b]	NP	206 (38.4)[c]	NP	≤42	EPDS	Symptoms/signs	Poor
			No	505	NP					NP	NP		NP		NP				
Zafar et al., 2015[48] (Pakistan)		528	Yes	89	NP			27.9 (5.1)	25.0 (6.0)	NP	NP	151 (25.8)[d]	NP	221 (37.8)[d]	NP				
			No	439	NP					NP	NP		NP		NP				
Meltzer-Brody et al., 2017[33] (Denmark)	Cohort	392,458	Yes	NP	983	x	√[a]	NP	NP	NP	NP	0 (0.0)	NP	NP	NP	≤365	ICD-10	ICD-10	Fair
			No	NP				NP	NP	NP	NP	0 (0.0)	NP	NP	NP				
Anjum & Batool, 2019[44] (Pakistan)	Cross-sectional	400	Yes	115	54	x	x	15–44	NP	NP	NP	NP	NP	238 (59.5)	NP	NP	EPDS	NP	Poor
			No	285	109				NP	NP	NP	NP	NP		NP	NP		NP	
Kountanis et al., 2020[45] (USA)	Cohort	390	Yes	57	10	x	x	31.0 (5.0)	31.7 (8.6)	26 (6.7)	23 (5.9)	104 (26.7)	23 (5.9)	NP	120 (30.8)	≤42	EPDS	NP	Fair
			No	333	52														
Liu, Yu, et al., 2021[49] (Sweden)	Cohort	486,722	Yes	31,663	630	x	√[a]	NP	NP	1237 (3.9)	3288 (10.4)	0 (0.0)	1237 (3.9)	NP	7865 (24.8)	≤365	ICD-10	ICD-10	Good
			No	455,059	8601			NP	NP	19,065 (4.2)	52,407 (4.2)	0 (0.0)	19,065 (4.2)	NP	61,474 (13.5)				
Parry-Smith et al., 2021[17] (UK)	Cohort	42,327	Yes	14,109	731	x	√	30.9 (5.7)	24.5 (7.0)	NP	NP	2110 (14.9)	NP	NP	5173 (36.7)	≤365	Read codes	ICD-10	Fair
			No	28,218	1309			30.8 (5.7)	24.1 (6.7)	NP	NP	4597 (16.0)	NP	NP	7020 (24.9)				
Tebeka et al., 2021[47] (France)	Case-control	3298	Yes	152	28	√	√	32.6 (NP)	NP	109 (3.0)	261 (7.9)	1165 (35)	NP	NP	817 (25%)	56	EPDS	NP	Poor
			No	3146	457				NP				NP	NP					
Wang et al., 2022[18] (China)	Cohort	7734	Yes	293	48	x	√	30.17 (4.5)	NP	NP	94 (32.1)	43 (14.7)	94 (32.1)	NP	164 (56.0)	42	EPDS	≥500 mL/24 h	Fair
			No	7441	906			29.41 (4.1)	NP	NP	2361 (31.7)	1245 (16.7)	2361 (31.7)	NP	2281 (30.7)				
Total	Cohort: 5 Cross-sectional: 2 Case-control: 2	934,432	Yes	46,508	1504	No/NP: 3 Yes for at least one: 6		30.6 (5.5)	24.3 (6.8)	20,439 (4.2)	58,434 (11.7)	9486 (1.7)	22,780 (4.6)	665 (43.7)	84,928 (15.7)	≤42: 4 >42: 4 NP: 1	EPDS: 6 ICD-10: 2 Codes: 1	ICD-10: 3 NP: 4 ≥500 mL/24 h: 1 Descriptive: 1	Poor: 3 Fair: 5 Good: 1
			No	495,466	11,441														

Abbreviations: BMI, body mass index; C-section, cesarean section; EPDS, Edinburgh Postnatal Depression Scales; ICD, International Classification of Diseases; NP, not provided; PPD, postpartum depression; PPH, exposure to postpartum hemorrhage; SD, standard deviation; UK, United Kingdom; USA, United States of America.

[a]No women with previous history of psychiatric disorders were included.

[b]Data available for 592 women.

[c]Data available for 537 women.

[d]Data available for 584 women.

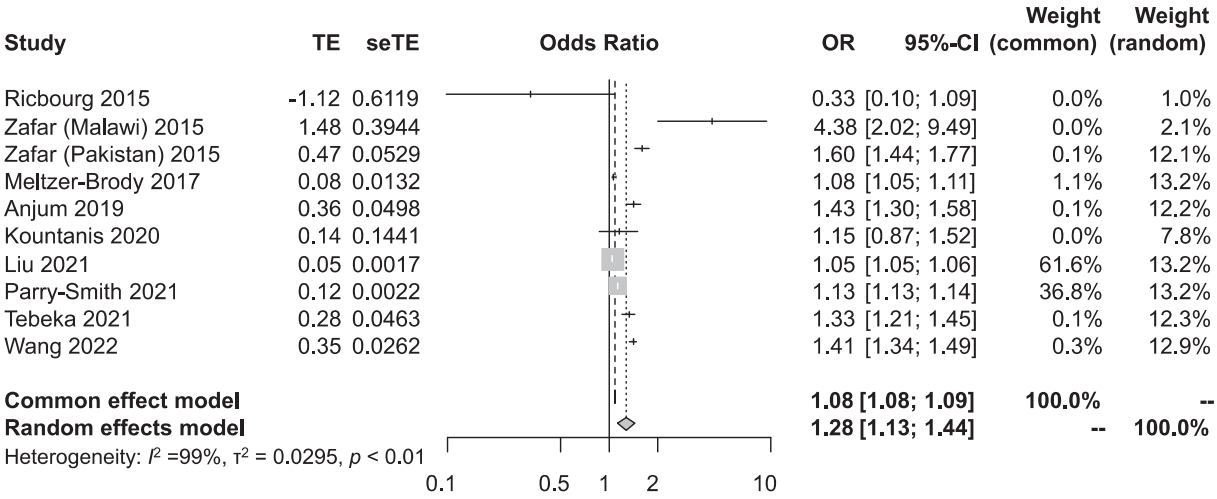

FIGURE 1 Odds Ratios (OR) of postpartum depression (PPD) in women with versus without postpartum hemorrhage (PPH).

TABLE 2 Meta-regression analyses.

	Co-efficient	Lower 95%CI	Upper 95%CI	*p*-value
Age	−0.11	−0.21	−0.01	**0.03***
BMI	−0.06	−0.21	0.10	0.49
Marital status	−0.08	−0.31	0.15	0.49
Education level	0.01	−0.003	0.01	0.30
History of depression/anxiety	0.01	0.002	0.01	**0.04***
Preeclampsia	−0.03	−0.11	0.06	0.52
Anemia during pregnancy	−0.02	−0.09	0.05	0.57
C-section	0.01	−0.003	0.01	0.19

Abbreviations: BMI, body mass index; CI, confidence interval; C-section, cesarean section.
*Statistically significant.

(estimated co-efficient −0.08, 95%CI = -0.31 to 0.15, $p = 0.49$), education level not higher than high school (estimated co-efficient 0.01, 95%CI = -0.003 to 0.01, $p = 0.30$), preeclampsia (estimated co-efficient −0.03, 95%CI = −0.11 to 0.06, $p = 0.52$), anemia during pregnancy (estimated co-efficient −0.02, 95%CI = -0.09 to 0.05, $p = 0.57$), and C-section (estimated co-efficient 0.01, 95%CI = -0.003 to 0.01, $p = 0.19$) (Table 2).

3.3.2 | Subgroup analyses

The Figure S3 shows the results of the subgroup analyses for samples assessed with standardized (or operationalized) PPH diagnostic criteria versus unstandardized or unspecified. We estimated lower ORs of PPD in women with PPH for studies using standardized PPH criteria compared to studies employing symptom description or not specifying on PPH assessment (OR = 1.42, 95%CI = 1.25 to 1.62, k = 6, n = 930,304, versus 1.16, 95%CI = 1.02 to 1.32, k = 4, n = 4128, $p = 0.03$). Apart from one study all other studies applied standardized criteria for PPD; after eliminating this study, we estimated an OR of 1.30 (95% CI = 1.13 to 1.50, k = 9, n = 892,105, $p < 0.001$). Further, the Figure S4 shows the results of the subgroup analyses based on the timepoint of PPD assessment; we estimated higher ORs of PPD in women with PPH for studies assessing PPD within 6 weeks after birth compared to studies assessing PPD longer than 6 weeks after birth although differences were not significant (OR = 1.41, 95%CI = 0.78 to 2.55, k = 5, n = 9227, versus 1.13, 95%CI = 1.03 to 1.24, k = 4, n = 925,205, $p = 0.47$). Additionally, the Figure S5 shows the results of the subgroup analyses for samples with versus without history of depression/anxiety and/or antidepressant treatment; we estimated significantly higher ORs of PPD in mixed samples consisting of women with history of depression/anxiety compared to women without history of depression/anxiety or antidepressant exposure (OR = 1.37, 95%CI = 1.18 to 1.60, k = 6, n = 55,212, versus 1.06, 95%CI = 1.04 to 1.09, k = 3, n = 879,220,

$p < 0.001$). Last, ORs of PPD for PPH were higher in studies from LMICs compared to studies assessing cohorts from non-LMICs (OR = 1.49, 95%CI = 1.37 to 1.61, k = 4, n = 9197, versus 1.13, 95%CI = 1.04 to 1.23, k = 6, n = 925,235, $p < 0.001$, Figure S6).

3.3.3 | Sensitivity analyses

In a sensitivity analysis excluding the three studies rated as of poor quality, we estimated an OR of 1.14 (95%CI = 1.02 to 1.29, k = 6, n = 929,671, $p = 0.02$) with heterogeneity remaining substantial ($I^2 = 99.3\%$, $\tau^2 = 0.01$). In the results of the sensitivity analysis excluding cross-sectional studies we estimated an OR of 1.17 (95%CI = 1.06 to 1.30, k = 7, n = 932,969, $p < 0.001$) with heterogeneity remaining substantial ($I^2 = 99.2\%$, $\tau^2 = 0.01$).

When sequentially excluding one study at a time, ORs did not substantially change (Table S2).

4 | DISCUSSION

Our systematic review and meta-analysis provides evidence of an elevated risk of PPD in women with PPH. Specifically, the risk of PPD was increased by 27% in women with PPH as compared to women without PPH. Using a previous ranking of PPD risk factors,[19] the OR of PPD associated with PPH is lower than the ORs of PPD for nine out of 12 other risk factors. Thus, the risk may not be substantial. Moreover, our findings suffered from substantial heterogeneity, which can be attributed to the diverging designs and methodological approaches. This heterogeneity also reflect the complexity of the interplay between PPH and PPD, which potentially contains multiple confounders[50]; specifically, there were different levels of adjustment for potential confounders between studies included. There was no single study simultaneously matching study groups for all well-known risk moderators, such as history of depression/anxiety or depression during pregnancy, peripartum anemia and mode of delivery. The use of standardized assessments for PPH essentially contributed to the variation with estimated ORs of PPD in studies employing standardized assessment being lower compared to studies using symptom description or unspecified assessments. Specifically, the risk of PPD was elevated by 42% in women without specified assessment or based on symptom description of PPH versus 16% in women with standardized assessments of PPH. Thus, future research may need to strongly embrace the use of standardized assessment of PPH.

We detected differences between studies exclusively investigating women with new incidence PPD and no previous antidepressant exposure compared to studies with mixed samples containing women with previous history of depression; the ORs of PPD were higher in the latter group implying some role for history of depression or depression during pregnancy in the pathway linking PPH and PPD. Specifically, in mixed samples of women with and without depression predating delivery the risk of PPD was increased by 44% in women with PPH compared to women without PPH. On the other hand, the PPD risk related to PPH was significantly increased by only 6% in women without history of depression or exposure to antidepressants. This suggests that history of depression or exposure to antidepressant could explain an essential part of the elevated PPD risk associated with PPH away, although the risk of PPD related to PPH remained significant in women without history of depression/anxiety or antidepressant treatment. As we did not have information on antidepressant exposure, it was not possible to disentangle effects of prenatal or antenatal depression and antidepressant exposure on the association between PPD and PPH. In fact, previous evidence suggested increased risk for PPH associated with sustained antidepressant exposure but also with the underlying depression or anxiety.[27,28] Within this context, the role of selective serotonin reuptake inhibitors (SSRIs) requires special focus. Indeed, SSRIs may affect platelet segregation and function, ultimately leading to increased risk of PPH[28]; preexisting SSRI treatment could be alternatively considered an index of history of depression/anxiety, so that it is ultimately hard to disentangle effects of SSRIs from the vulnerability due to earlier mental distress. Nevertheless, the increased PPH-related PPD risk is also in full alignment with moderating effects of history of depression/anxiety reported in our meta-regression analysis.

Previous epidemiological evidence has suggested wide disparities regarding incidence of PPH and related complications between cohorts from LMICs and non-LMIC[7]; our subgroup analysis reported higher ORs of PPH-related PPD in cohorts from LMICs versus non-LMICs. A potential explanation of this difference may be a severity bias of PPH reported in LMICs given barriers to care for women with PPH in LMICs compared to non-LMICs.[7] Our meta-regression analysis also suggested higher ORs of PPD in women versus without PPH being moderated by younger study sample age. This counterintuitive finding may be driven by the unusually high OR of PPD associated with PPH in the Malawi cohort of Zafar and associates.[48] Women in this cohort were considerably younger compared to all other samples of studies included in our meta-analysis; indeed, authors specified that there were six girls aged 15 years old and several other girls younger than 18 years in the sample.[48] Early

motherhood has been previously strongly associated with severe PPH[49]; the consequences of severe PPH include serious adverse maternal outcomes,[51] that may underlie the PPD risk. Additionally, among risk factors for severe PPH,[52] assisted fertilization and peripartum anemia are also risk factors for PPD.[19] Apart from potential age effects, the Malawi cohort had a high incidence of human immunodeficiency virus (HIV) (≈16%)[48]; these women are also likely to experience intimate partner violence.[53] Ultimately, this cohort may substantially differ from the other included cohorts.

Quality issues may have led to a slight overestimation of PPD risk in women with versus without PPH; in fact, the sensitivity analysis excluding poor-quality studies yielded a PPD risk lower than in the main analysis (14% vs. 28%). The studies included in the sensitivity analysis had matched study groups for at least one potential confounder; thus, it can be suggested that the risk of PPD might have been even lower if proper matching and confounders had been considered. The design might have also confounded some effects, as none of the cross-sectional studies were included in this sensitivity analysis.

To the best of our knowledge, this is the first effort to meta-analyze evidence on PPH and PPD. Our meta-analysis included the largest sample on women with or without PPH and PPD, with almost one million women, and thus with sufficient power to study postpartum outcomes. An increased risk of PPD was observed in women with PPH. High clinical priority must be given to women with PPH given the maternal outcomes potentially including PPD. History of depression/anxiety may, at least partially, account for the association between PPD and PPH.

These results need to be interpreted with caution. First, an amount of valuable information was not available and therefore could not be inserted in our analysis; for example, information on the volume of blood loss was available only in two studies,[18,46] whereas no study specified on primary or secondary PPH. Moreover, there was very limited information on antidepressant treatment in women with depression/anxiety during pregnancy. Thus, no conclusions on the role of antidepressant treatment can be drawn. Future research will need to expand on moderators of the PPD risk associated with PPH. Adding data on novel moderators will enable a more reliable detection of women with PPH more likely to develop PPD. Second, the included studies were exclusively observational, they do not allow hypotheses on causality, but only on associations.[54] Third, matching among women with and without PPH for severe confounders was performed only for a small number of crucial factors.[55] Fourth, the substantial heterogeneity in this meta-analysis was one of the major limitations, although, our subgroup and sensitivity analyses partially accounted for the heterogeneity. Fifth, data on the PPH-associated risk of PPD mainly derived from cohorts from high-income countries; nevertheless, there are wide disparities regarding the incidence of PPH and PPH-related complications between high- and middle-/low-income countries (LMICs)[7]; therefore, data on the association between PPH and PPD from LMIC cohorts are urgently required.

To conclude, here we investigated the risk of PPD in women with PPH, which affects up to one tenth of women giving birth.[2] Our findings suggest that women with PPH are at greater PPD risk, although the risk for new-onset PPD may be not essentially elevated. Earlier psychiatric comorbidities may substantially moderate the risk of PPD associated with PPH. Perinatal screening tools, such as the list of risk factors developed by the American College of Obstetricians and Gynecologists should include items regarding PPH,[56] whereas women with PPH should be monitored closely. The cohort of women with PPH and history of depression/anxiety or antidepressant treatment should be given special attention not only for the risk of obstetric complications, but also for the risk of developing PPD.

AUTHOR CONTRIBUTIONS

Chiara Gastaldon, Sebastian Olbrich, Nicole Ochsenbein-Koelble, Corrado Barbui, Erich Seifritz, Georgios Schoretsanitis contributed to the design of the study. Chiara Gastaldon, Georgios Schoretsanitis performed the search and collected the data. Chiara Gastaldon and Georgios Schoretsanitis performed the statistical analysis. All authors analyzed the data. Chiara Gastaldon and Georgios Schoretsanitis drafted the manuscript and all other authors revised the manuscript. All authors contributed to and approved the paper.

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Drs. Gastaldon, Ochsenbein-Koelble and Barbui do not report any conflict of interest. Dr. Schoretsanitis has served as a consultant for HLS Therapeutics and Thermo Fisher and has received speaker's fees from HLS

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PEER REVIEW

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ETHICS STATEMENT

Not applicable.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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