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Causes of and risk factors for postpartum haemorrhage: a systematic review and meta-analysis



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Summary

Background An understanding of the causes of postpartum haemorrhage is needed to provide appropriate treatment and services. Knowledge of the risk factors for postpartum haemorrhage can help address modifiable risk factors. We did a systematic review and meta-analysis to identify and quantify the various causes and risk factors for postpartum haemorrhage.

Methods In this systematic review and meta-analysis, we did a systematic literature search in MEDLINE, Embase, Web of Science, Cochrane Library, and Google Scholar for cohort studies of postpartum haemorrhage from Jan 1, 1960, to Nov 30, 2024 without language restrictions. At least two authors independently undertook study selection, data extraction, and quality assessment. Population-based cohort studies available in English were eligible. Rates of postpartum haemorrhage causes as well as crude and adjusted odds ratios (ORs) for risk factors were pooled using a random-effects model. Risk factors were classified as having weak, moderate, or strong association based on the pooled ORs: weak (OR >1 to 1.5), moderate (OR >1.5 to 2), and strong (OR >2). This study is registered with PROSPERO, CRD42023479686.

Findings We synthesised data from 327 studies, including 847 413 451 women with no restriction on age, race, or ethnicity. Most studies were of high methodological quality. The pooled rates of the five commonly reported causes of postpartum haemorrhage were uterine atony (70.6% [95% CI 63.9–77.3]; n=834 707 women, 14 studies), genital tract trauma (16.9% [9.3–24.6]; n=18 449 women, six studies), retained placenta (16.4% [12.3–20.5]; n=235 021 women, nine studies), abnormal placentation (3.9% [0.1–7.6]; n=29 638 women, two studies), and coagulopathy (2.7% [0.8–4.5]; n=236 261, nine studies). The pooled rate of women with multiple postpartum haemorrhage causes was 7.8% (95% CI 4.7–10.8; n=666, two studies). Risk factors with a strong association with postpartum haemorrhage included anaemia, previous postpartum haemorrhage, caesarean birth, female genital mutilation, sepsis, no antenatal care, multiple pregnancy, placenta praevia, assisted reproductive technology use, macrosomia with a birthweight of more than 4500 g, and shoulder dystocia. Risk factors with moderate association with postpartum haemorrhage included BMI ≥ 30 kg/m², COVID-19 infection, gestational diabetes, polyhydramnios, pre-eclampsia, and antepartum haemorrhage. Risk factors with weak association with postpartum haemorrhage included Black and Asian ethnicity, BMI 25–29.9 kg/m², asthma, thrombocytopenia, uterine fibroids, antidepressant use, induction of labour, instrumental birth, and premature rupture of membranes.

Interpretation The finding that uterine atony is the commonest cause of postpartum haemorrhage supports the WHO recommendation for all women giving birth to be given prophylactic uterotonics. Knowledge of risk factors with a strong association with postpartum haemorrhage can help to identify women at high risk of postpartum haemorrhage who could benefit from enhanced prophylaxis and treatment. The importance of multiple concurrent causes of postpartum haemorrhage supports the use of treatment bundles.

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Introduction

Postpartum haemorrhage is a common cause of maternal mortality worldwide, accounting for an estimated 27% of all maternal deaths.^{1,2} The commonly used definition of postpartum haemorrhage is blood loss of 500 mL or more within the first 24 h after birth.³ An understanding of the causes and risk factors might contribute to efforts to reduce stagnant mortality rates from postpartum haemorrhage.

Known causes of postpartum haemorrhage include uterine atony, genital tract trauma, retained placenta, abnormal placentation, and coagulopathy. However, prevalence of these causes is poorly understood. Knowing the rates of the causes of postpartum haemorrhage and the burden they represent allows for the planning and resourcing of health-care services to provide appropriate management. Previous studies have identified uterine atony as being the commonest cause.^{4,5} Confirming this,

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Research in context

Evidence before this study

Postpartum haemorrhage is a leading cause of maternal mortality worldwide. Updated synthesised data are needed to guide global policy on risk stratification and mitigation, as well as postpartum haemorrhage prevention and treatment. We searched MEDLINE, Web of Science, Embase, Cochrane Library, and Google Scholar from Jan 1, 1960, to Nov 30, 2024, without language restrictions, using the search term “postpartum haemorrhage” in the title and abstract, and as a MeSH term. We identified 22 studies for the rate of postpartum haemorrhage causes and 311 studies assessing risk factors for postpartum haemorrhage. Most of the included studies were of high methodological quality.

Added value of this study

Our systematic review and meta-analysis produced up-to-date evidence-based pooled rates of causes of postpartum haemorrhage, and severe and refractory postpartum haemorrhage. Uterine atony, which the majority of first-line postpartum haemorrhage treatments target, was the commonest cause. Other important causes were genital tract trauma, retained placenta, abnormal placentation, and

coagulopathy. We highlighted the importance of multiple concurrent causes resulting in postpartum haemorrhage. A range of risk factors and their levels of association with postpartum haemorrhage were identified. Many of these are modifiable. Risk factors with a strong association with postpartum haemorrhage included anaemia, previous postpartum haemorrhage, caesarean birth, female genital mutilation, sepsis, no antenatal care, multiple pregnancy, placenta praevia, assisted reproductive technology use, fetal macrosomia with birthweight more than 4500 g, and shoulder dystocia.

Implications of all the available evidence

Knowledge of postpartum haemorrhage causes and risk factors can allow policy makers to promote effective prophylaxis and treatment, particularly for women at high risk for postpartum haemorrhage, and develop strategies to target the risk factors. Postpartum haemorrhage caused by multiple concurrent causes supports the use of treatment bundles. Practices associated with reduced risks of postpartum haemorrhage, such as skin-to-skin contact and breastfeeding, should be promoted.

and determining the rate of atony as a cause, will focus attention on adequately resourcing treatments, such as uterotonics and uterine tamponade devices. Similarly, knowing the contribution of the other causes, such as coagulopathy, will allow for adequate planning and provision of their treatments.⁶

There are numerous well established risk factors for postpartum haemorrhage, such as obesity, anaemia, history of previous postpartum haemorrhage, and caesarean birth.⁷ Some of these risk factors are modifiable (ie, they encompass behaviours and conditions that can be altered or controlled to reduce the risk of postpartum haemorrhage). Knowledge of their level of association with postpartum haemorrhage can help target strategies to mitigate their effect. It can also help to identify individuals at high risk of postpartum haemorrhage who might require closer monitoring as well as enhanced prophylaxis and treatment. New risk factors for postpartum haemorrhage have also been identified, including COVID-19 infection⁸ and antidepressant use.⁹ Knowing their level of association could provide the opportunity to modify their effects through strategies such as vaccination, in the prevention of COVID-19 disease, and monitoring of clotting profile, in the case of antidepressant use.

The existing literature encompasses systematic reviews concerning causes of and risk factors for postpartum haemorrhage, but these are either narrow in their scope, or out of date.¹⁰ Some reviews have restricted their scope to vaginal birth,¹¹ others to severe postpartum haemorrhage,⁷ and others to specific causes, such as atonic postpartum haemorrhage.¹²

We, therefore, did a comprehensive systematic review and meta-analysis to identify and quantify the rates of different causes of postpartum haemorrhage, as well as the association of a wide range of risk factors for postpartum haemorrhage at vaginal and caesarean birth.

Methods

Search strategy and selection criteria

For this systematic review and meta-analysis, we followed PRISMA reporting guidelines.¹³ This study is registered with PROSPERO, CRD42023479686. Population-based cohort studies (ie, regional, national, multicountry, or multicentre studies) that reported the causes and risk factors for postpartum haemorrhage were eligible. Unpublished papers, preprints, editorials, comments, letters, case reports, books, and non-human and non-English language studies were excluded. We also excluded review papers, but we did assess their reference lists for potentially eligible studies. Five electronic databases were searched (MEDLINE, Web of Science, Embase, Cochrane Library, and Google Scholar). Grey literature was identified using Google Scholar. The reference lists of the included studies and available reviews were checked to identify further eligible studies. The search strategy used the keywords “postpartum haemorrhage” in the title and abstract and as a MeSH term to identify eligible studies using a comprehensive search string (appendix p 1). The search results were restricted to papers published between Jan 1, 1960, and Nov 30, 2024.

Five authors (MAI, IY, KNS, SSA, and SK) independently screened studies, initially by title and

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See Online for appendix

abstract, followed by a full-text review, if appropriate, to determine eligibility for inclusion. Any differences over inclusion were resolved by consensus or by discussion with other review authors (AC, AJD, and IG).

Data extraction from the final selection of studies was undertaken independently by two authors (MAI and IY). When duplicate data from the same source population were found, the older study data were removed. The following data and information were extracted from each eligible study using a pre-piloted data extraction table: first author's last name, publication year, country, study duration, number of women, study design, population, risk factors studied, definition of postpartum haemorrhage and severe postpartum haemorrhage, blood loss measurement method (subjective or objective), and confounders for which adjustment was made. Subjective measurement methods were based on visual estimation, whereas objective methods were based on volumetric (eg, calibrated blood collection drape or tray) or gravimetric (eg, weighing blood-soaked swabs, pads, linen, or blood collected in drape or pouch) approaches.

The included studies generally defined postpartum haemorrhage as blood loss of 500 mL or more in the first 24 h after birth, and severe postpartum haemorrhage as blood loss of 1000 mL or more in the first 24 h after birth. Studies which did not state the exact volume of blood loss for their definition of postpartum haemorrhage and severe postpartum haemorrhage were still eligible for inclusion. Refractory postpartum haemorrhage was defined as haemorrhage that required second-line treatments, such as additional uterotonics or bimanual uterine compression.¹⁴ We grouped severe postpartum haemorrhage and refractory postpartum haemorrhage together as they overlap substantially, and both require second-line treatments.

The methodological quality of included studies was evaluated by three authors independently (MAI, IY, and SSA) by applying the Joanna Briggs Institute (JBI) critical appraisal tool for cohort studies.¹⁵ The JBI tool uses 11 quality checklist items with four options: yes, no, unclear, and not applicable. One point is given for each response of yes. The total percentage of yes responses was used to determine the final score. The evidence provided by each study for our research question was classified as high quality (low risk of bias: >80% yes responses), moderate quality (moderate risk of bias: 60–80% yes responses), or low quality (high risk of bias: <60% yes responses). Any disagreements were resolved after discussion with other authors (AC and IG). We explored publication bias by generating funnel plots of comparisons that had ten or more studies. We visually assessed the funnel plots for asymmetry (appendix pp 188–91).

Data analysis

The pooled rates for the different causes of postpartum haemorrhage, and severe and refractory postpartum haemorrhage, and the 95% CIs were calculated using a

random-effects model. For each of the risk factors, adjusted odds ratios (ORs), controlling for confounders (appendix pp 2–96), were extracted from individual studies along with corresponding 95% CIs. Additionally, the raw aggregate data were extracted from every individual study included in the analysis to obtain unadjusted associations that were pooled using the Mantel-Haenszel method (random-effects model). Our choice of using a random-effects model, was based on an expectation that exposures are unlikely to be truly identical across included studies.¹⁶ The figures in our results present both adjusted ORs and crude ORs, where these were available. The text manuscript prioritises the reporting of adjusted ORs but presents crude ORs when the relevant adjusted ORs were unavailable. For risk factors where the crude OR was significant ($p < 0.05$), but the adjusted OR was not, we present both the crude OR and adjusted OR in the text.

The risk factors for postpartum haemorrhage were grouped into the following categories to allow for meaningful comparison: demographic, lifestyle, medical, past and current pregnancy-related, and labour-related and birth-related. We classified the level of association of each risk factor with postpartum haemorrhage into weak (OR >1 to 1.5), moderate (OR >1.5 to 2), and strong (OR >2) based on the adaptations by Shih and colleagues.¹⁷

Heterogeneity of the studies was assessed by visualisation of the forest plots and calculation of the τ^2 statistic (on the log odds scale).

When there were fewer than two studies for a particular comparison, we were unable to do a meta-analysis, and so we summarised the findings and presented the data in relevant forest plots. These are provided in the appendix (pp 109–87).

All statistical analyses were carried out using STATA version 18 or Review Manager version 5.4.1. We used STATA to generate the rates of causes of postpartum haemorrhage, and severe and refractory postpartum haemorrhage, with their 95% CIs. Review Manager was used to generate crude estimates and 95% CIs for the various risk factors. STATA was used for the adjusted risk factor estimates with 95% CIs.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

We identified 25 343 studies, from which 12 202 ineligible studies were excluded as they were case reports, book chapters, comments, editorials, non-English language manuscripts (or manuscripts not available as English language translations), non-human studies, review papers, or duplicate studies. The remaining 13 141 studies were screened based on their titles and abstracts. After full-text screening of 610 studies, 327 studies were

included in the analysis: 22 studies that evaluated postpartum haemorrhage causes, and 311 studies that evaluated risk factors. Of these, six studies contributed data to both the causes and risk factor analyses (figure 1).^{14,18–22}

Nine of the included studies were conducted across multiple countries, whereas the remainder (318 studies) were based in a single country. The most common study countries were the USA (81 studies), China (36 studies), the UK (20 studies), Israel (18 studies), Australia (13 studies), Canada (13 studies), Sweden (11 studies), India (ten studies), Ethiopia (nine studies), and France (eight studies; appendix pp 2–96). There was substantial representation from both high-income countries (HICs), and low-income and middle-income countries (LMICs; appendix p 108).

Of the 327 studies analysed, 70 (21.4%) were prospectively designed, whereas 257 (78.6%) were conducted retrospectively (appendix pp 2–96). Only 12 (3.7%) of the included studies used an objective measurement method to measure postpartum blood loss. The remainder relied on visual estimation.

The results of the JBI risk of bias assessments¹⁵ showed that 310 (94.8%) of the included studies were high quality (low risk of bias), 17 (5.2%) were moderate quality (moderate risk of bias), and none were low quality (high risk of bias; appendix pp 97–106).

Uterine atony was the commonest cause of postpartum haemorrhage. The pooled rate for uterine atony as a cause for postpartum haemorrhage was 70.6% (95% CI 63.9–77.3; n=834707 women, 14 studies). The pooled rates for the other causes were as follows: genital tract trauma, 16.9% (95% CI 9.3–24.6; 18449 women, six studies); retained placenta, 16.4% (12.3–20.5; 235021 women, nine studies); abnormal placentation, 3.9% (0.1–7.6; 29638 women, two studies); and coagulopathy, 2.7% (0.8–4.5; 236261 women, nine studies). The pooled rate for multiple causes (two or more concurrent causes) was 7.8% (95% CI 4.7–10.8; 666 women, two studies; figure 2).

Uterine atony was also the commonest cause of severe and refractory postpartum haemorrhage. However, its pooled rate as a cause for severe and refractory postpartum haemorrhage was less than that for postpartum haemorrhage at 41.4% (95% CI 34.9–47.9; 80110 women, six studies). The pooled rates for the other causes of severe and refractory postpartum haemorrhage were as follows: genital tract trauma, 12.8% (95% CI 5.8 to 19.8; 80110 women, six studies); retained placenta, 13.8% (8.1 to 19.4; 80110 women, six studies); abnormal placentation, 8.8% (–2.1 to 19.8; 42915 women, four studies); and coagulopathy, 1.1% (–0.2 to 2.4; 3681 women, two studies). The pooled rate for multiple causes with severe and refractory postpartum haemorrhage was 27.4% (95% CI 22.8 to 32.0; 361 women, one study; figure 3).

There were no demographic or lifestyle risk factors for postpartum haemorrhage with a strong association (ie,

OR >2). The demographic and lifestyle factors with a moderate association were BMI of 30.0–34.9 kg/m² compared with BMI of 18.5–24.9 kg/m² (adjusted OR 1.51 [95% CI 1.32–1.72]; 3409963 women, ten studies). The demographic and lifestyle factors with a weak association with postpartum haemorrhage were BMI of 25.0–29.9 kg/m² compared with BMI of 18.5–24.9 kg/m² (adjusted OR 1.21 [95% CI 1.13–1.30]; 3409963, ten studies); Asian ethnicity compared with White ethnicity (1.15 [1.04–1.27]; 2598284 women, three studies); and Black ethnicity compared with White ethnicity (1.44 [1.03–2.01]; 2598284, three studies; figure 4).

Skin-to-skin contact and breastfeeding had an adjusted OR of less than 1 when its association with postpartum haemorrhage was estimated: (adjusted OR 0.55 [95% CI 0.42–0.73]; 7548 women, one study; figure 4).

The medical risk factors for postpartum haemorrhage that showed a strong association with postpartum haemorrhage were anaemia (adjusted OR 2.36 [95% CI 1.29–4.32]; 167573 women, two studies), female genital mutilation (adjusted OR 2.14 [95% CI 1.43–3.20];

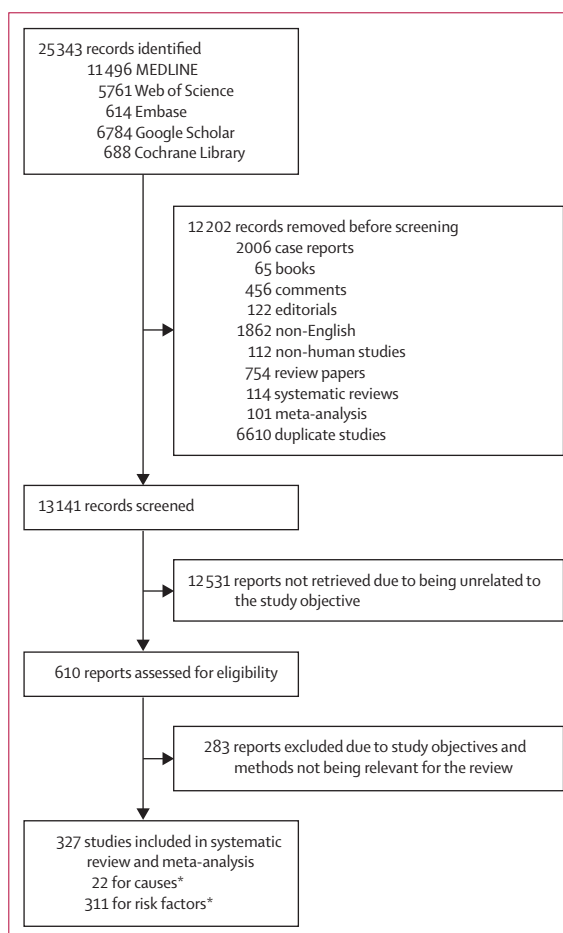


Figure 1: Study selection

*Six of the included studies had data for both causes and risk factors.

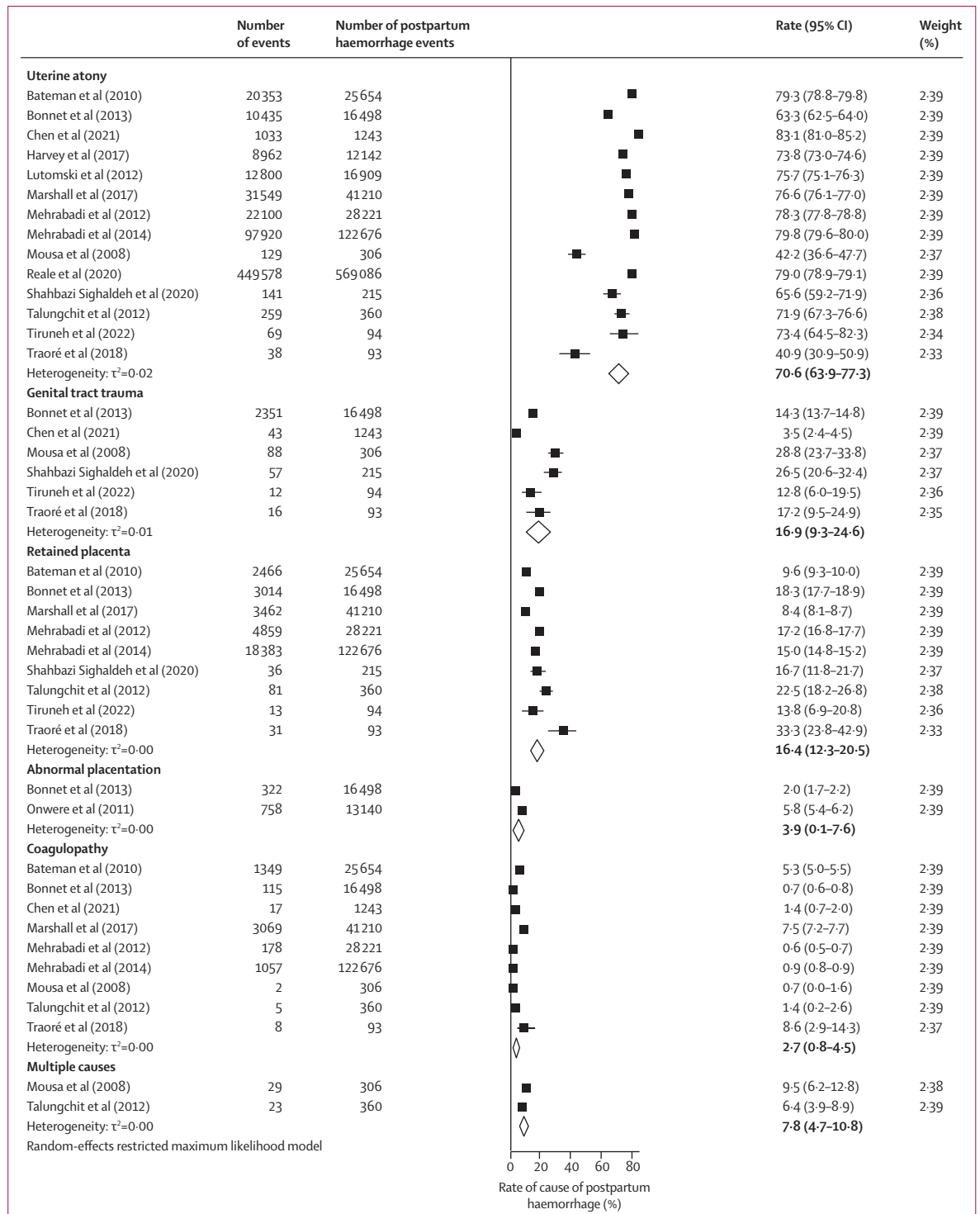


Figure 2: Rates of causes of postpartum haemorrhage

40 157 women, five studies), liver cirrhosis (crude OR 4.43 [95% CI 3.20–6.13]; 8186 women, four studies), sepsis (adjusted OR 2.31 [95% CI 1.55–3.46]; 10 619 435 women, three studies), suicidal behaviour (adjusted OR 2.11

[95% CI 1.58–2.83]; 23 696 522 women, two studies; appendix pp 107–08), tuberculosis (crude OR 2.39 [95% CI 2.25–2.54]; 57 393 459 women, one study), and venous thromboembolism (adjusted OR 4.38 [95% CI

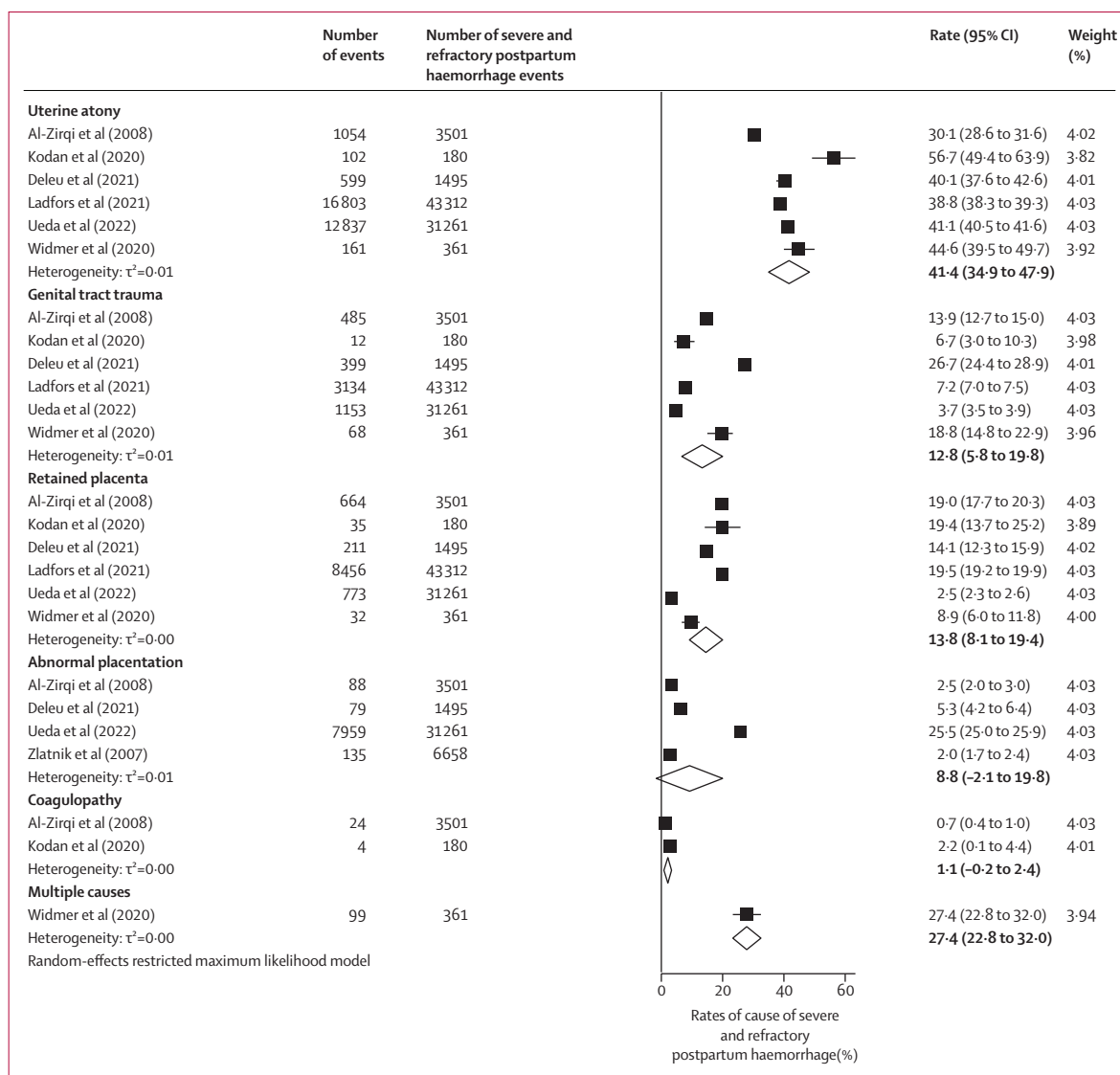


Figure 3: Rates of causes of severe and refractory postpartum haemorrhage

1.75–10.97]; 772 women, one study). The medical risk factors showing a moderate association were COVID-19 (adjusted OR 1.85 [95% CI 1.56–2.18]; 323 959 women, five studies), Ehlers-Danlos syndrome (adjusted OR 1.66 [95% CI 1.09–2.52]; 14 513 666 women, two studies), gestational diabetes (crude OR 1.88 [95% CI 1.16–3.03]; 4679 women, six studies), liver disease (crude OR 1.64 [95% CI 1.12–2.42]; 18 650 041 women, ten studies), pancreatitis (adjusted OR 1.90 [95% CI 1.55–2.33]; 13 815 919 women, one study), polyhydramnios (adjusted OR 1.73 [95% CI 1.32–2.28]; 107 350 women, three studies), pre-eclampsia (adjusted OR 1.54 [95% CI 1.48–1.60]; 1697 353 women, three studies), and von Willebrand disease (crude OR 1.52 [95% CI 1.29–1.80]; 601 959 women, two studies; adjusted OR 3.82 [95% CI 0.78–18.70]; 66 women, one study). The medical risk

factors showing a weak association were hypothyroxinaemia (crude OR 1.32 [95% CI 1.05–1.66]; 7051 women, one study; adjusted OR 1.29 [95% CI 0.98–1.69]; 7051 women, one study), asthma (adjusted OR 1.24 [95% CI 1.13–1.36]; 82 900 342 women, three studies), psoriasis (adjusted OR 1.40 [95% CI 1.04–1.89]; 2 350 330, one study), thrombocytopenia (adjusted OR 1.40 [95% CI 1.04–1.89]; 233 681 women, three studies), uterine fibroids (adjusted OR 1.20 [95% CI 1.06–1.35]; 113 984, one study), vitamin D insufficiency (adjusted OR 1.07 [95% CI 1.03–1.12]; 399 women, one study); antidepressant use overall (adjusted OR 1.47 [95% CI 1.28–1.70]; 764 865 women, six studies), cannabis use disorder (adjusted OR 1.09 [95% CI 1.08–1.11]; 73 109 790 women, one study), opioid use disorder (adjusted OR 1.16 [95% CI 1.14–1.19];

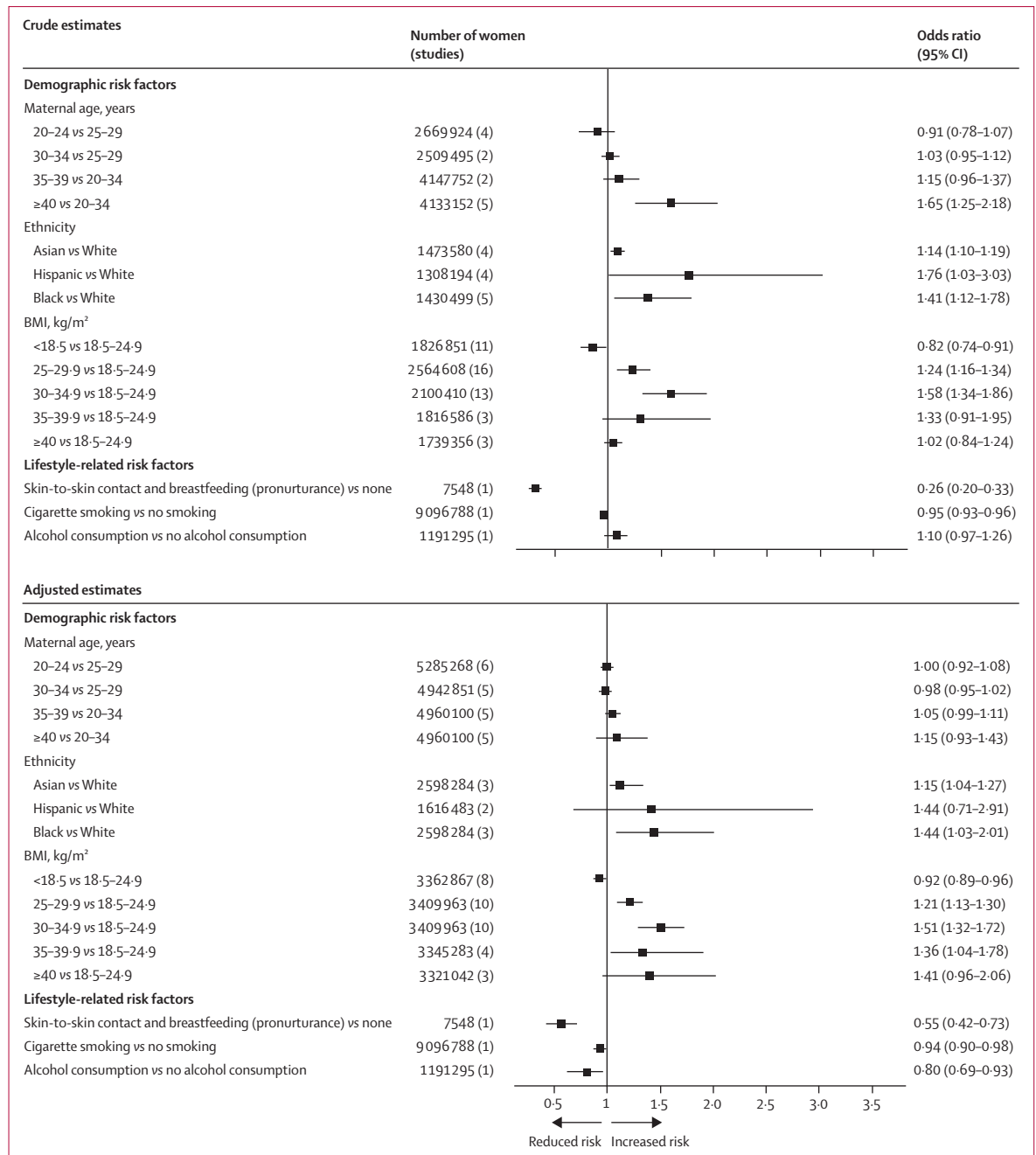


Figure 4: Demographic and lifestyle-related risk factors for postpartum haemorrhage

73 109 790 women, one study), and codeine use (adjusted OR 1.20 [95% CI 1.06–1.35]; 67 982 women, one study; figure 5).

Results for pregnancy-related risk factors for postpartum haemorrhage are shown in figure 6. The pregnancy-related risk factors with a strong association were previous postpartum haemorrhage (adjusted OR 3.17 [95% CI 2.42–4.16]; 1137 846 women, four studies), previous stillbirth (2.31 [1.44–3.71];

3476 women, one study), no antenatal care visits (2.78 [1.78–4.36]; 2083 women, three studies), incarcerated uterus (2.80 [1.79–4.38]; 9096 788 women, one study), multiple pregnancy (5.86 [5.50–6.25]; 210 132 women, one study), placenta praevia (3.10 [1.61–5.97]; 512 289 women, four studies), resolved placenta praevia (3.35 [2.43–4.62]; 1706 women, two studies), assisted reproductive technology use (2.40 [2.08–2.76]; 21 657 010 women, 16 studies), and frozen embryo transfer

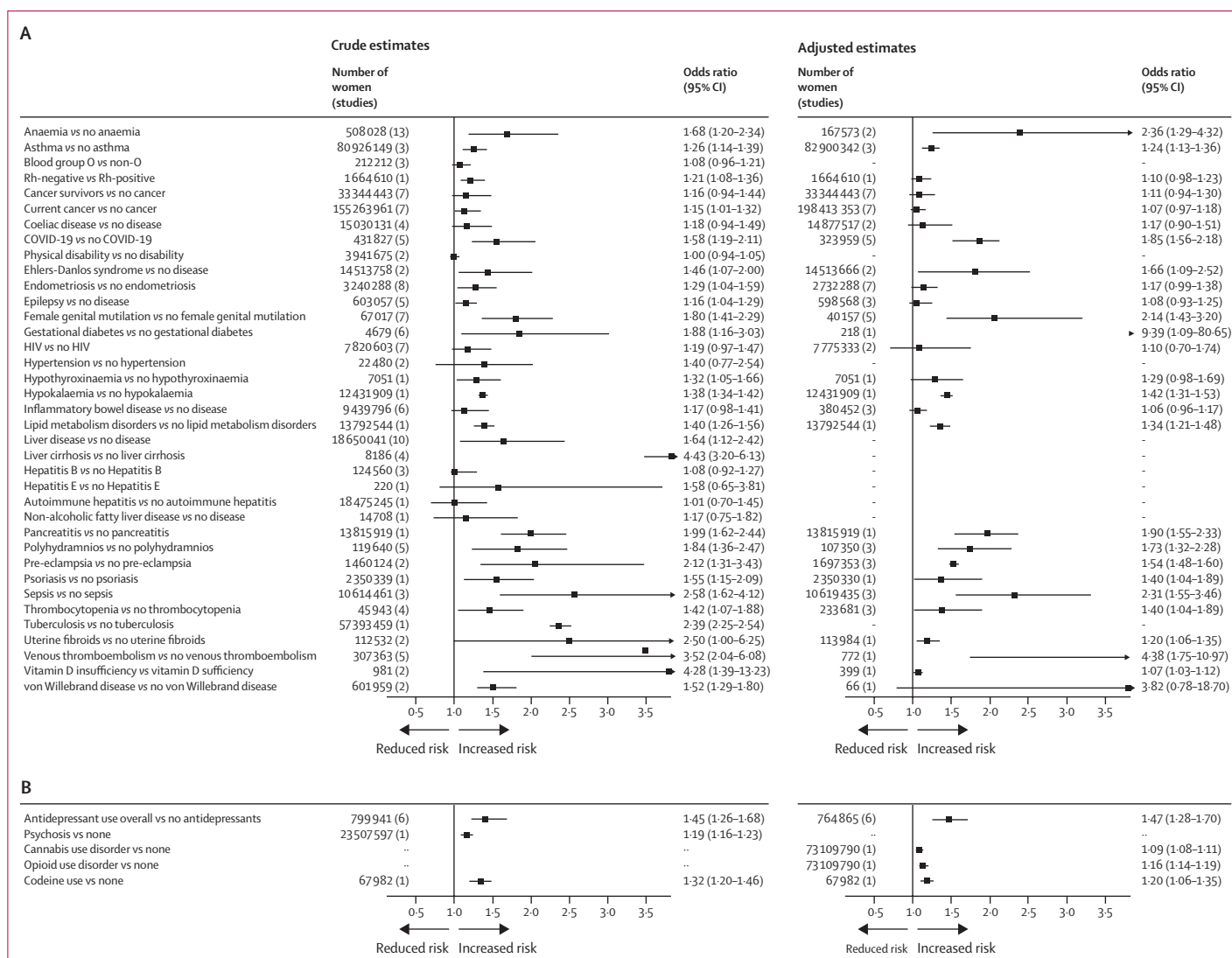


Figure 5: Medical risk factors (A and B) for postpartum haemorrhage

in programming cycles versus frozen embryo transfer in natural cycles (2.65 [2.23-3.14]; 30615 women, two studies). The pregnancy-related risk factors with a moderate association were antepartum haemorrhage (crude OR 2.09 [95% CI 0.74-5.89]; adjusted OR 1.94 [95% CI 0.69-5.44]; 229232 women, two studies) and medical termination of pregnancy versus surgical termination of pregnancy (adjusted OR 1.71 [95% CI 1.26-2.31]; 45632 women, one study; appendix pp 107-08). The pregnancy-related risk factors with a weak association were previous medical termination of pregnancy versus primigravid women (adjusted OR 1.48 [95% CI 1.20-1.83]; 45632 women, one study) and grand multiparous versus multiparous (1.20 [1.10-1.30]; 290572 women, one study; appendix pp 107-08).

The labour and birth risk factors for postpartum haemorrhage with a strong association were caesarean

birth (adjusted OR 5.18 [95% CI 3.42-7.85]; 1014 women, one study), fetal macrosomia with birthweight ≥ 5000 g (adjusted OR 3.25 [95% CI 1.30-8.14]; 215492 women, two studies), fetal macrosomia with birthweight 4500-4999 g (adjusted OR 2.08 [95% CI 1.70-2.54]; 277097 women, four studies), and shoulder dystocia (crude OR 2.06 [95% CI 1.67-2.54]; 177937 women, two studies). The labour and birth risk factor with a moderate association was fetal macrosomia with birthweight 4000-4499 g (adjusted OR 1.67 [95% CI 1.54-1.80]; 277097 women, four studies). The following labour and birth risk factors had a weak association with postpartum haemorrhage: induction of labour (adjusted OR 1.37 [95% CI 1.22-1.54]; 295053 women, nine studies), instrumental birth (adjusted OR 1.44 [95% CI 1.03-2.00]; 1166162, three studies), and premature rupture of membranes (crude OR 1.39 [95% CI 1.28-1.51]; 108689 women, two studies; figure 7).

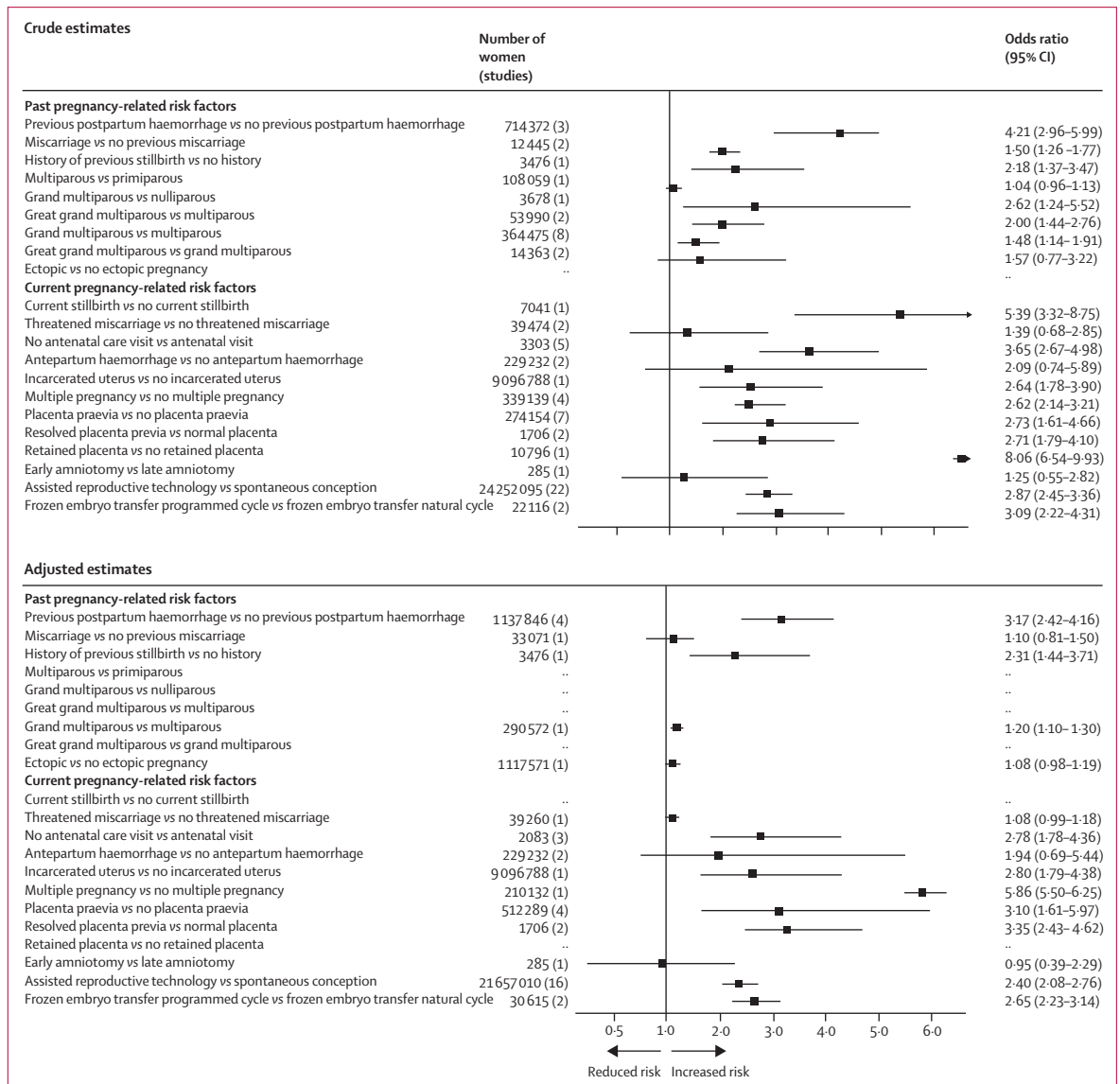


Figure 6: Pregnancy-related risk factors for postpartum haemorrhage

We present additional risk factors for postpartum haemorrhage in the appendix (pp 107–08). Forest plots representing the crude and adjusted ORs for all identified risk factors for postpartum haemorrhage are presented in the appendix (pp 109–87).

We were unable to perform subgroup analyses for the causes of postpartum haemorrhage by mode of birth (vaginal birth vs caesarean birth) as only a limited number of our included studies disaggregated data for mode of birth. Most studies provided combined data for vaginal and caesarean birth.

For most risk factors, we were unable to undertake subgroup analyses by income setting (HIC vs LMIC), due to a paucity of available data. However, we did have data to undertake subgroup analyses for BMI 25–29.9 kg/m²

compared with BMI 18.5–24.9 kg/m², and assisted reproductive technology compared with spontaneous conception. In both cases, there was no significant difference between subgroups by income setting (appendix p 192). We were unable to undertake subgroup analyses by country due to insufficient data to generate subgroups with enough studies to allow reliable analysis.²³

Discussion

We identified a range of risk factors and their levels of association with postpartum haemorrhage. We found that the pooled rates for the causes of postpartum haemorrhage, for which we were able to identify data, showed that uterine atony was the commonest cause. This finding is consistent with previously published data,¹⁰ and supports

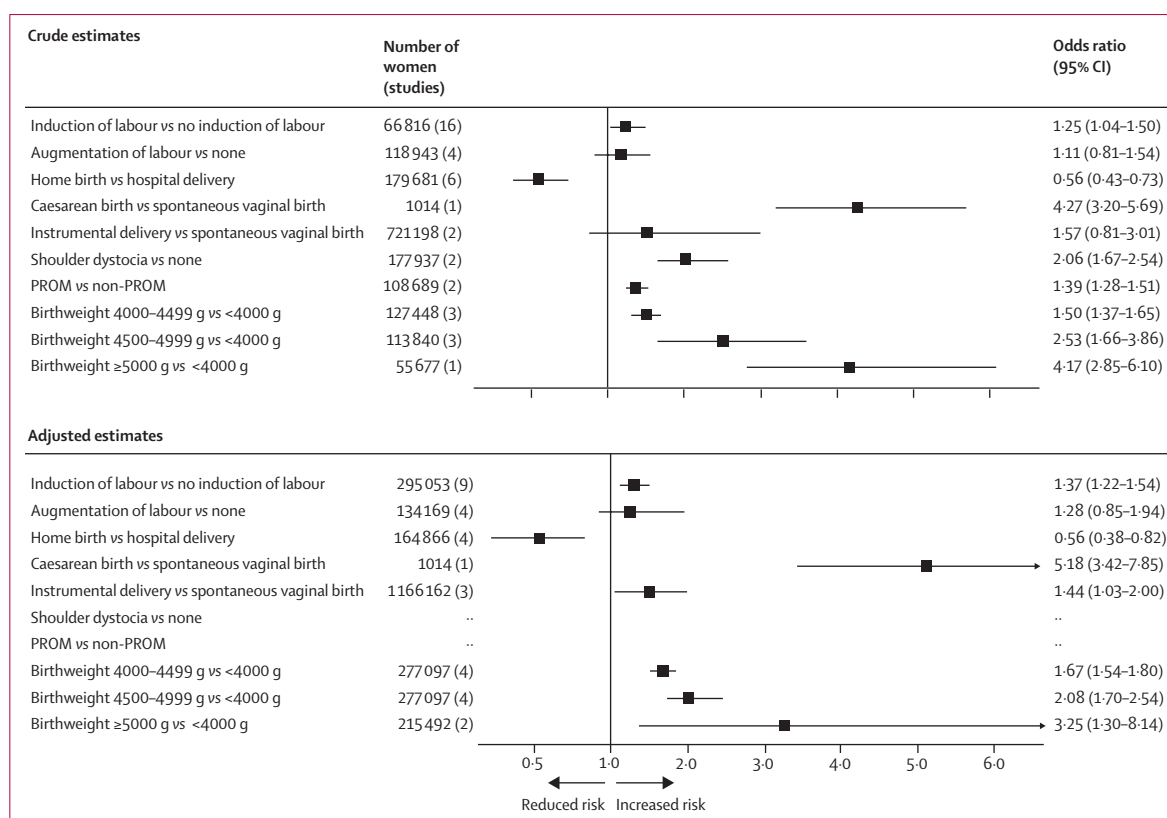


Figure 7: Labour and birth risk factors for postpartum haemorrhage
 PROM=premature rupture of membrane.

the global recommendations for all women giving birth to be given prophylactic uterotonics for postpartum haemorrhage prevention.²⁴ The other causes of postpartum haemorrhage, in descending order of frequency, were genital tract trauma, retained placenta, abnormal placentation, and coagulopathy. The results showed that multiple causes (two or more concurrent causes) were also important for causing postpartum haemorrhage. This finding lends itself to the use of treatment bundles in the management of postpartum haemorrhage to address several causes that might coexist. One such bundle is the MOTIVE bundle that provides first-response treatment regardless of the cause of bleeding.²⁵

The results for the pooled rates of causes in severe postpartum haemorrhage and refractory postpartum haemorrhage showed that atony was still the commonest cause, but to a lesser extent than for postpartum haemorrhage. Severe and refractory postpartum haemorrhage generally occur after initial postpartum haemorrhage treatments, which mainly focus on the management of atony; therefore, it is expected that atony will have a diminished representation in those who continue to bleed beyond initial postpartum haemorrhage treatments.

Our review identified both modifiable and non-modifiable risk factors for postpartum haemorrhage.

Modifiable risk factors allow for lifestyle factor adjustments and correction of deficiencies to potentially lessen their impact. For non-modifiable risk factors, health-care providers might improve outcomes with advanced planning of care, enhanced postpartum haemorrhage prophylaxis, and prompt postpartum haemorrhage treatment.

Modifiable risk factors associated with postpartum haemorrhage in our review included high BMI, anaemia, hypertension, vitamin D insufficiency, cannabis and opioid use, and the absence of antenatal care.

Our study showed a biological gradient for the association of BMI and postpartum haemorrhage. Higher BMI categories had stronger associations with postpartum haemorrhage. It is important to consider regional variations with different cutoff values for BMI categories. The health implications of cutoff values for BMI categories for Asian populations, for example, are different to those for European populations.²⁶

An estimated 37% of pregnant women globally are anaemic.²⁷ Anaemia impacts a pregnant women's ability to cope with complications such as postpartum haemorrhage, infection, and cardiovascular compromise. Iron deficiency is a leading cause of anaemia, and nutrition programmes for pregnant women might help to reduce its effect.²⁷ The association of anaemia

and postpartum haemorrhage might be due to compensatory increased placental size and vascularity,²⁸ or due to decreased myometrial strength seen in iron deficiency states,²⁹ both of which increase the likelihood of bleeding.

The association of no antenatal care with postpartum haemorrhage highlights the importance of providing regular antenatal care to pregnant women to identify other risk factors, such as high BMI, anaemia, and history of previous postpartum haemorrhage.³⁰ Once identified, these risk factors can be addressed through lifestyle and dietary advice in the case of high BMI, and correction of deficiencies in the case of anaemia due to iron deficiency. Knowledge of a previous history of postpartum haemorrhage may necessitate closer monitoring of women giving birth.

We highlighted several underlying medical conditions with an association with postpartum haemorrhage, which if optimised might reduce the chances of postpartum haemorrhage occurring. These included gestational diabetes, asthma, venous thromboembolism, and COVID-19 infection. The association of gestational diabetes with postpartum haemorrhage in some women might be due to it being a risk factor for macrosomia,³¹ which itself is a risk factor for postpartum haemorrhage. Asthma is known to be associated with other risk factors for postpartum haemorrhage, such as hypertension and obesity.³² The treatment of venous thromboembolism involves administration of anticoagulants, which can increase the risk of bleeding. This reason might account for the association of venous thromboembolism with postpartum haemorrhage. COVID-19 infection results in a prothrombotic state. Despite this, it is associated with an increased risk of postpartum haemorrhage. This association might be due to the administration of anticoagulants for the treatment of COVID-19 in patients, which can increase the risk of bleeding. As the COVID-19 pandemic was limited to a restricted time period, it represents an exceptional scenario, which might be less applicable in the future.

We highlighted antidepressant use as an example of a non-modifiable risk factor with an association with postpartum haemorrhage. Antidepressants such as selective serotonin reuptake inhibitors cause serotonin depletion in platelets and hinder blood clotting,⁹ therefore increasing the likelihood of bleeding. Pregnant women taking such medication might need closer monitoring of their blood clotting profile.

Risk factors that had an association with a reduced likelihood of postpartum haemorrhage included skin-to-skin contact and breastfeeding. Both result in endogenous oxytocin release, which causes contraction of the uterus and reduces bleeding.³³ For smoking and alcohol consumption, the estimates were from one study each. The adjusted and crude ORs for smoking, and the adjusted OR for alcohol consumption, showed an association with a reduced likelihood of postpartum

haemorrhage. However, there was discordance between the adjusted and crude ORs for alcohol consumption.

The adjusted ORs in our study did not show a significant association between maternal age and postpartum haemorrhage. This finding contrasts with that of a previous study,³⁴ which showed an association between increasing maternal age and complications such as postpartum haemorrhage.

Strengths of our review included the comprehensive and broad search strategy, which identified several large cohort studies. This approach allowed us to pool rates across local, regional, and national levels. Despite searching databases as far back as 1960, only two of our included studies were published before 2000, and so our findings are based on more recent evidence. We performed quality assessment using the established JBI quality assessment tool¹⁵ and found that most studies were of high methodological quality. We identified no studies of low methodological quality. Our analyses included several large studies, so we used τ^2 rather than I^2 when assessing heterogeneity. In meta-analyses, values of τ^2 generally remain unchanged as precision (the size of the included studies) increases, whereas the values of I^2 can quickly increase towards 100% and create challenges for interpretation.³⁵ We categorised the strength of the associations of the various risk factors with postpartum haemorrhage by adapting the methods of Shih and colleagues,³⁷ who established the following categories: strong association (OR >2) and weak association (OR >1 to 2). We subdivided the weak association category into weak (OR >1 to <1.5) and moderate categories (OR >1.5 to 2). This approach allowed us to distinguish risk factors with strong, moderate, and weak associations with postpartum haemorrhage.

A limitation of most of the studies included in our analysis is the use of subjective visual estimation of blood loss to quantify postpartum haemorrhage. Visual estimation has been shown to be inaccurate, and so these studies might not accurately capture the true rate of postpartum haemorrhage.³⁶ A large international, cluster-randomised trial²⁵ investigating postpartum haemorrhage highlighted the importance of objective blood loss measurement to accurately diagnose postpartum haemorrhage and allow its prompt management. The definitions of postpartum haemorrhage and severe postpartum haemorrhage used by different studies included in our review sometimes varied. For our analysis, we relied on each individual paper's stated definition of postpartum haemorrhage and severe postpartum haemorrhage. With regard to the factors used by different studies to adjust their findings and generate adjusted ORs, although common factors were adjusted for, with maternal age being the commonest, these factors did vary. This variation might have reduced precision when adjusted ORs were pooled. For some of the risk factors we identified, we only had data from a single study, and occasionally a single, small study. We

recognise that in such situations we might have unreliable estimates. These estimates are mainly presented in the appendix.

Not all of the risk factors we identified act independently. Often risk factors might act through other connected risk factors, as aforementioned in the case of gestational diabetes and macrosomia. Other risk factors that might be linked include macrosomia and shoulder dystocia, and antepartum bleeding and anaemia. Reducing the effect of one risk factor might be helpful in reducing the effects of other connected risk factors.

Another limitation of our review was the inability to disaggregate data for vaginal and caesarean births for the causes of postpartum haemorrhage. Only a few primary studies that looked at causes of postpartum haemorrhage separated the rates of postpartum haemorrhage for vaginal and caesarean birth. The rates of causes of postpartum haemorrhage and the associations of risk factors for postpartum haemorrhage might be different for these two modes of birth.

Our review restricted eligible studies to those available in English. We did not apply a language filter, but instead excluded studies at the title and abstract screening stage. This approach allowed us to include studies that had originally been published in languages other than English, but were then translated and made available in English. Excluding non-English language studies might have reduced the number of studies from, for example, French, Spanish, and Chinese speaking countries. However, we had substantial study representation from non-English language speaking countries.

It is important to consider the prevalence of risk factors in conjunction with the strength of their association with postpartum haemorrhage when planning policy. Incarcerated uterus had a strong association with postpartum haemorrhage, but it is much rarer than a risk factor such as Black ethnicity, which although weakly associated with postpartum haemorrhage, presents a greater global health burden due to its higher prevalence.

Women who have risk factors with a strong association with postpartum haemorrhage, such as anaemia, history of postpartum haemorrhage, and caesarean birth, can be identified and prioritised for specific prevention and treatments. WHO currently recommends oxytocin as the uterotonic agent of choice for postpartum haemorrhage prevention for all births.²⁴ However, there are other uterotonic agents, such as the combinations of ergometrine plus oxytocin and misoprostol plus oxytocin, which are more effective but have higher rates of side-effects.³⁷ There has been reluctance to routinely give all women these more effective agents due to the concerns about side-effects. However, it might be appropriate to offer these agents to women identified as being at high risk for postpartum haemorrhage, due to the presence of risk factors with a strong association with postpartum haemorrhage, despite their increased risk of side-effects.

Future research should identify risk factors for specific conditions, such as placenta spectrum disorder, and severe and refractory postpartum haemorrhage. Identifying risk factors for severe and refractory postpartum haemorrhage could allow for the anticipation of escalation of care in these cases.

In summary, the synthesis of the available data in this systematic review and meta-analysis highlights the rates of causes of postpartum haemorrhage and identifies several important risk factors and their strength of association with postpartum haemorrhage. Risk factors with a strong association include anaemia, previous postpartum haemorrhage, caesarean birth, female genital mutilation, sepsis, no antenatal care, multiple pregnancy, placenta praevia, assisted reproductive technology use, macrosomia with birthweight more than 4500 g, and shoulder dystocia. This information can be used to allocate appropriate resources to tackle the causes of postpartum haemorrhage, identify women at high risk of postpartum haemorrhage, optimise the modifiable risk factors for postpartum haemorrhage, and mitigate the non-modifiable risk factors.

Contributors

IY drafted the manuscript. IY, MAI, AJD, JZ, IG, MJP, and AC contributed to the study design and methodology. MAI, IY, and KNS conducted the primary literature search, data extraction, and synthesis of results. SSA, SK, MP, and K-MM assisted in the literature search and data extraction. IY, AJD, IG, and AC resolved conflicts regarding study inclusion and data extraction. JZ and MJP conducted the statistical analysis. AJD and KNS assisted with production of figures. All authors contributed to critical revision of the manuscript for important intellectual content and gave final approval for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

Data in this systematic review and meta-analysis are extracted from published studies available elsewhere. All processed data are presented in this Article and the appendix.

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