Journal of the American Heart Association

SYSTEMATIC REVIEW AND META-ANALYSIS

Impact of Chronic Hypertension and Antihypertensive Treatment on Adverse Perinatal Outcomes: Systematic Review and Meta-Analysis

Sukainah Y. Al Khalaf, MPH; Éilis J. O'Reilly, ScD; Peter M. Barrett, MB, MFPHMI; Debora F. B. Leite, PhD; Lauren C. Pawley, MSc; Fergus P. McCarthy, PhD*; Ali S. Khashan, PhD*

BACKGROUND: Maternal chronic hypertension is associated with adverse pregnancy outcomes. Previous studies examined the association between either chronic hypertension or antihypertensive treatment and adverse pregnancy outcomes. We aimed to synthesize the evidence on the effect of chronic hypertension/antihypertensive treatment on adverse pregnancy outcomes.

METHODS AND RESULTS: Medline/PubMed, EMBASE, and Web of Science were searched; we included observational studies and assessed the effect of race/ethnicity, where possible, following a registered protocol (CRD42019120088). Random-effects meta-analyses were used. A total of 81 studies were identified on chronic hypertension, and a total of 16 studies were identified on antihypertensive treatment. Chronic hypertension was associated with higher odds of preeclampsia (adjusted odd ratio [aOR], 5.43; 95% CI, 3.85–7.65); cesarean section (aOR, 1.87; 95% CI, 1.6–2.16); maternal mortality (aOR, 4.80; 95% CI, 3.04–7.58); preterm birth (aOR, 2.23; 95% CI, 1.96–2.53); stillbirth (aOR, 2.32; 95% CI, 2.22–2.42); and small for gestational age (SGA) (aOR, 1.96; 95% CI, 1.6–2.40). Subgroup analyses indicated that maternal race/ethnicity does not influence the observed associations. Women with chronic hypertension on antihypertensive treatment (versus untreated) had higher odds of SGA (aOR, 1.86; 95% CI, 1.38–2.50).

CONCLUSIONS: Chronic hypertension is associated with adverse pregnancy outcomes, and these associations appear to be independent of maternal race/ethnicity. In women with chronic hypertension, those on treatment had a higher risk of SGA, although the number of studies was limited. This could result from a direct effect of the treatment or because severe hypertension during pregnancy is a risk factor for SGA and women with severe hypertension are more likely to be treated. The effect of antihypertensive treatment on SGA needs to be further tested with large randomized controlled trials.

Key Words: antihypertensive ■ chronic hypertension ■ fetal outcome ■ meta-analysis ■ neonatal outcome ■ pregnancy ■ systematic review

Chronic hypertension refers to high blood pressure predating pregnancy or recognized before 20 weeks' gestation,[1] and is estimated to affect 1% to 5% pregnancies.[2–5] The prevalence of chronic hypertension in pregnancy increases with increasing maternal age, obesity, diabetes mellitus, and medical comorbidities in pregnancy,[6–10] and has nearly doubled in the United States from 1990 to 2009, especially among Black women.[3,11]

Chronic hypertension has previously been associated with increased risk of adverse pregnancy outcomes. A systematic review and meta-analysis that

Correspondence to: Sukainah Y. Al Khalaf, MPH, School of Public Health, Fourth Floor, Western Gateway Building, Western Road, University College Cork, Cork, Ireland. E-mail: alkhalaf.sukainah@gmail.com

Supplementary Material for this article is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.120.01849

*Dr McCarthy and Dr Khashan contributed equally to this work and are co–senior authors.

For Sources of Funding and Disclosures, see page 14.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- This systematic review and meta-analysis summarized the literature on the effect of maternal chronic hypertension and antihypertensive treatment on adverse pregnancy outcomes.
- Women with chronic hypertension in pregnancy had higher risk of adverse maternal, fetal, and neonatal outcomes than normotensive women; no evidence was found to suggest that maternal race/ethnicity modified these associations.
- In women with chronic hypertension, women on antihypertensive treatment may have a higher risk of small-for-gestational age infants than untreated women.

What Are the Clinical Implications?

- Antihypertensive treatment during pregnancy in women with chronic hypertension did not appear to reduce the risk of adverse fetal and neonatal outcomes.
- This study supports the need of large trials to examine the benefits and potential harms of antihypertensive treatment in pregnant women with chronic hypertension.

Nonstandard Abbreviations and Acronyms

PTB	preterm birth

included 55 studies reported an increase in pooled incidence of adverse pregnancy outcomes among women with chronic hypertension.[12] However, this review did not make a direct comparison between hypertensive and normotensive women from available literature; instead, the pooled incidences of adverse pregnancy outcomes among women with chronic hypertension were compared with the US general population. This review also did not examine the role of antihypertensive treatment or race/ethnic origin.

Minimizing episodes of severe hypertension during pregnancy is critical to reduce the risk of associated maternal complications, including stroke.[13] Whether certain antihypertensive agents may reduce the risk of adverse pregnancy outcomes in addition to controlling maternal hypertension is unclear.[14] A small number of antihypertensive agents are used to treat hypertension in pregnancy and in the postpartum period. Others are contraindicated because of potential teratogenicity.[5,15] First-line agents for the treatment of hypertension in pregnancy include labetalol, methyldopa, and nifedipine, but there is limited evidence to suggest whether any agent performs better in reducing the occurrence of adverse pregnancy outcomes.[5,15,16]

Previous reviews investigated the effect of either chronic hypertension or antihypertensive treatment, whereas we synthesized the evidence of both on a longer list of adverse pregnancy outcomes in finer detail (eg, we looked at subtypes of preterm birth [spontaneous, indicated, or not specified]). Also, as part of this review, we aimed to summarize the gaps and limitations in previous literature. Therefore, we conducted this systematic review and meta-analysis of observational studies to estimate the effect of chronic hypertension/antihypertensive treatment on maternal, fetal, and neonatal outcomes, taking into account, where possible, whether maternal race/ethnicity or type of antihypertensive agent modified these associations.

METHODS

Registration and Reporting

The protocol for this review was registered on The International Prospective Register of Systematic Reviews (identifier: CRD42019120088).[17] We followed the Preferred Reporting Items for Systematic Review and Meta-Analysis guidelines for all procedures and reporting.[18] The authors declare that all supporting data are available within the article and its supplementary material.

Ethical Approval

Ethical approval was not necessary as this systematic review relied completely on published articles.

Information Sources and Search Strategy

This systematic review and meta-analysis comprised 2 separate comprehensive searches of the same databases. Electronic search was conducted through PubMed/Medline, Embase, and Web of Science. In addition, the bibliographies of previous systematic reviews and all identified studies were searched for further potentially relevant articles.

Search 1: Identifying Studies on Chronic Hypertension

The first search focused mainly on identifying studies assessing the association between maternal chronic hypertension and adverse perinatal outcomes. We searched the databases from inception through January 2019. We used a combination of subject headings and Medical Subject Headings terms, and keywords related to (1) pregnant women with chronic hypertension (exposed group); (2) normotensive pregnant women (nonexposed group); and (3) maternal,

fetal, and neonatal complications (outcomes). The search terms we used for retrieving relevant articles are shown in Data S1.

Search 2: Identifying Studies on Antihypertensive Treatment

Similarly, we searched the same databases from inception through May 2019. The search strategy captured: (1) pregnant women with chronic hypertension on antihypertensive treatment (exposed group); (2) untreated pregnant women (nonexposed group); and (3) maternal, fetal, and neonatal complications (outcomes). The search strategy we used is shown in Data S2. We did not restrict the second search to women with chronic hypertension when assessing the effect of antihypertensive treatment because some studies of treatment effect used normotensive women as the comparison, but in the analysis we grouped studies that reported the effect of treatment for chronic hypertension separately.

Outcome Measures

The maternal outcomes were preeclampsia, cesarean section, postpartum hemorrhage, hemolysis, elevated liver enzyme levels, and low platelet levels, and maternal mortality. Fetal and neonatal outcomes were miscarriage, stillbirth, preterm birth (PTB) <37 weeks' gestation, very PTB <34 weeks' gestation, small for gestational age (SGA), low birth weight (LBW), neonatal intensive care unit admission, neonatal death, and perinatal death.

Selection Process and Eligibility Criteria

Two investigators (S.A.K. and P.B.) independently screened titles and abstracts, excluding studies that clearly did not meet the predefined criteria. Then, the full texts of potentially eligible studies were obtained. We included cohort and case-control studies and excluded randomized controlled trials (RCTs), case reports, case series, editorials, reviews, conference abstracts, book chapters, and animal/in vitro studies. When ≥2 studies were included in the same cohort, we included the one with the largest population. We excluded studies that by design enrolled women with chronic hypertension and additional comorbidities and studies with participant numbers <25 pregnant women with chronic hypertension.

Data Collection Process and Quality Assessment

An electronic standardized data extraction form was developed and pilot tested on 7 studies before beginning data extraction. One investigator (S.A.K.) extracted the data for all included studies, and 2 investigators (F.M.C. and D.F.B.L.) extracted the data independently for >50% of the included studies, selected randomly, to ensure the validity of extracted data. We extracted data on year of publication, country, setting, sample size and eligibility criteria, source of data, exposure and outcome definitions, reported effect measures (if not reported, we use raw data to calculate odds ratios [ORs]), statistical tests or models, and confounder adjusted for, if any. We used the Newcastle-Ottawa Scale to assess the study quality, as recommended by recent guidelines to evaluate the quality of cohort and case-control studies.[19] The Newcastle-Ottawa Scale uses a "star system," in which stars are assigned to show higher quality based on 3 criteria: selection of the study groups; comparability of the groups; and the ascertainment of the exposure and/or outcome of interest (the total score ranged from 0 to 9, where 0 is the lowest). The quality assessments were performed independently by 2 investigators (S.A.K. and L.P.). In addition, a third investigator (A.S.K.) resolved any inconsistencies between the 2 investigators about included articles, data extraction, and quality assessment (more details about the methods are available in Data S2).

Statistical Analysis

First, we assessed the effect of chronic hypertension, compared with normotensive women (reference group), on the previously mentioned adverse maternal, fetal, and neonatal outcomes.

Then, we conducted separate meta-analyses that included studies that stratified the associations by maternal race/ethnicity to assess effect modification. The subgroup meta-analysis calculates the effects within each subgroup level and then compares the pooled effect estimates for each subgroup. The *P* value from the Cochran Q test, test for interaction, was used to determine whether the magnitude of the effect of chronic hypertension differs according to maternal race/ethnicity. Sensitivity analyses were performed by study design (case-control/cohort), study location (North America/Europe/Australia/other), and decade of publication (1990–1999/2000–2009/2010–2019).

Second, we assessed the effect of antihypertensive treatment on the same outcomes. The comparative groups in these analyses divided into 2 categories: (1) untreated normotensive women; and (2) untreated women with chronic hypertension. Sensitivity analyses were performed to assess the effect of different types of antihypertensive agent, including women who were exposed to β-blockers only versus untreated women; and women exposed to centrally acting antiadrenergic agent only versus untreated women.

In these meta-analyses, we included studies with different populations in different countries and at different time frames; thus, the true impact of chronic hypertension/antihypertensive treatment on adverse pregnancy outcomes might differ from study to study. Therefore, random-effects models were selected, which accounts for both random variability and the variability in effects among the studies, to account for any remaining heterogeneity in the estimates across studies.[20] The study estimates, both crude and adjusted ORs (aORs), and their SEs (calculated from CIs) were meta-analyzed on the log OR scale. The weight given to each study is the inverse of the variance of the effect estimate, where larger studies are given more weight than smaller studies.[21,22] Combined results were presented as a pooled OR with 95% CIs; and for adjusted estimates, we followed the authors' definitions of adjustment.

Heterogeneity among studies was measured using the I^2 statistic and categorized as low (I^2<25%), medium (I^2=25%–50%), or high (I^2>50%), whereas publication bias was assessed using the Begg funnel plot and the Egger test when there were ≥10 studies in a meta-analysis.[23,24] A statistically significant *P* value was based on a threshold of <0.05. Data were analyzed using Review Manager Software (version 5.3)[25] and Stata/MP software (version 16) for the Egger test.

RESULTS

Search Results and Study Characteristics

This systematic review and meta-analysis summarized information from 94 studies. The selection process for the first (chronic hypertension) and second (antihypertensive treatment) reviews is illustrated in Figures 1 and 2, respectively. For chronic hypertension, the initial search identified 9739 studies, of which 81 articles were included.[3,9,26–104] For antihypertensive treatment, 8629 citations were identified initially, and a total of 16 articles were included.[35,45,60,105–117] Three studies reported data on both exposures (chronic hypertension and antihypertensive treatment).[37,46,60] Of the 94 studies, 80 were cohort studies, and 14 were case-control studies.

Among studies that reported antihypertensive treatment as an exposure, 6 of 16 studies examined the effect of treatment among women with chronic hypertension compared with untreated normotensive women.[35,45,105–107,117] Eight studies compared the outcomes in women with chronic hypertension (treated versus untreated),[60,108–114] whereas the remaining 2 studies compared the effect of different antihypertensive agents among women with chronic hypertension.[115,116]

Details about individual studies, including exposures and outcomes definitions, are presented in Tables S1 through S27 and Figures S1 through S26. Moreover, the definitions for outcomes varied across the included studies. For example, 19 studies defined SGA as birth weight <10th percentile for gestational age; 5 studies defined SGA as birth weight <5th percentile for gestational age; 3 studies did not report the definitions used; and another 3 studies used *International Classification of Diseases, Ninth Revision* (*ICD-9*), codes (Table S9).

Level of Agreement, Publication Bias, and Quality Assessment

The level of agreement was high (>80%) between investigators in the selection process, data extraction, and quality assessment. For publication bias, the results indicated that bias may not be a substantial problem as funnel plots (for preeclampsia [Figure S1B]; cesarean section [Figure S3C]; PTB [Figure S6C]; stillbirth [Figure S8C]; SGA [Figure S9B], and LBW [Figure S10B]) show approximately symmetric distributions, and the results of the Egger test were nonsignificant (*P* values=0.65; 0.92; 0.14; 0.47; 0.29; and 0.09, respectively), suggesting that the published literature does not have publication bias. The total scores for studies' quality of Newcastle-Ottawa grading ranged from 4 to 9, with poorer quality among studies examining the effect of antihypertensive treatment.

Results of Meta-Analysis

The impact of maternal chronic hypertension compared with normotensive women. The prevalence of chronic hypertension among cohort participants ranged from 0.3%[42] to 4.3%[51] across studies. Maternal chronic hypertension was associated with higher adjusted odds of preeclampsia (adjusted OR [aOR], 5.43; 95% CI, 3.85–7.65); hemolysis, elevated liver enzyme levels, and low platelet levels (aOR, 3.08; 95% CI, 1.79–5.30); cesarean section (aOR, 1.87; 95% CI, 1.61–2.16); postpartum hemorrhage (aOR, 1.46; 95% CI, 1.17–1.81); maternal mortality (aOR, 4.80; 95% CI, 3.04–7.58), very PTB (aOR, 1.92; 95% CI, 1.09–3.38); and PTB (aOR, 2.23; 95% CI, 1.96–2.53) (Table 1 and Figure 3[3,26–45,97,98]). We further divided the PTB into unspecified, spontaneous, and medically indicated; both crude and adjusted analyses showed 4 times greater odds of medically indicated PTB (aOR, 4.67; 95% CI, 3.55–6.14). Conversely, we found no statistically significant association between chronic hypertension and spontaneous PTB (aOR, 1.44; 95% CI, 0.74–2.80) (Figure S8A and S8B). We additionally excluded studies with multiple pregnancies and that did not affect the results for PTB and very PTB. We found higher odds of SGA (aOR, 1.96; 95% CI, 1.61–2.40) and LBW (aOR, 3.05;

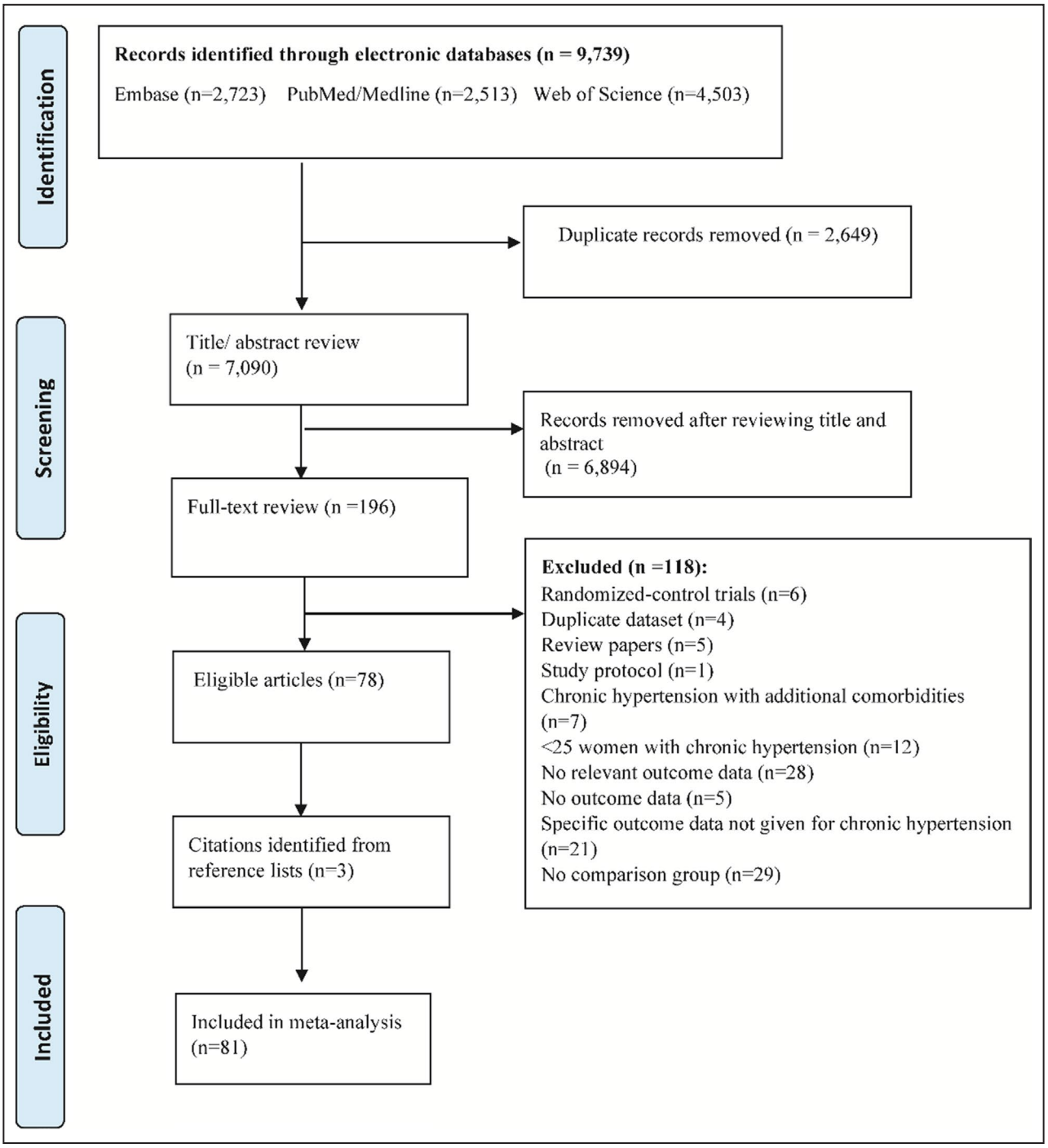


Figure 1. Preferred Reporting Items for Systematic Review and Meta-Analysis flow diagram of studies of chronic hypertension in pregnancy.

95% CI, 2.24–4.15) among mothers with chronic hypertension (Figure 4[1]). Similarly, stillbirth (aOR, 2.32; 95% CI, 2.22–2.42), neonatal death (aOR, 2.29; 95% CI, 2.02–2.59), and perinatal death (aOR, 1.87; 95% CI, 1.33–2.63) were associated with maternal chronic hypertension. One study on miscarriage (aOR, 1.33; 95% CI, 0.90–1.97) and another on neonatal intensive care unit admission (aOR, 1.37; 95% CI, 1.05–1.79) supported an association with chronic hypertension.

The results of subgroup analyses on chronic hypertension and adverse outcomes by maternal race/ethnicity showed that the odds of PTB among

*References 3, 9, 26, 32, 34, 42, 43, 45, 50, 56, 59, 60, 69, 72–79, 81–89.

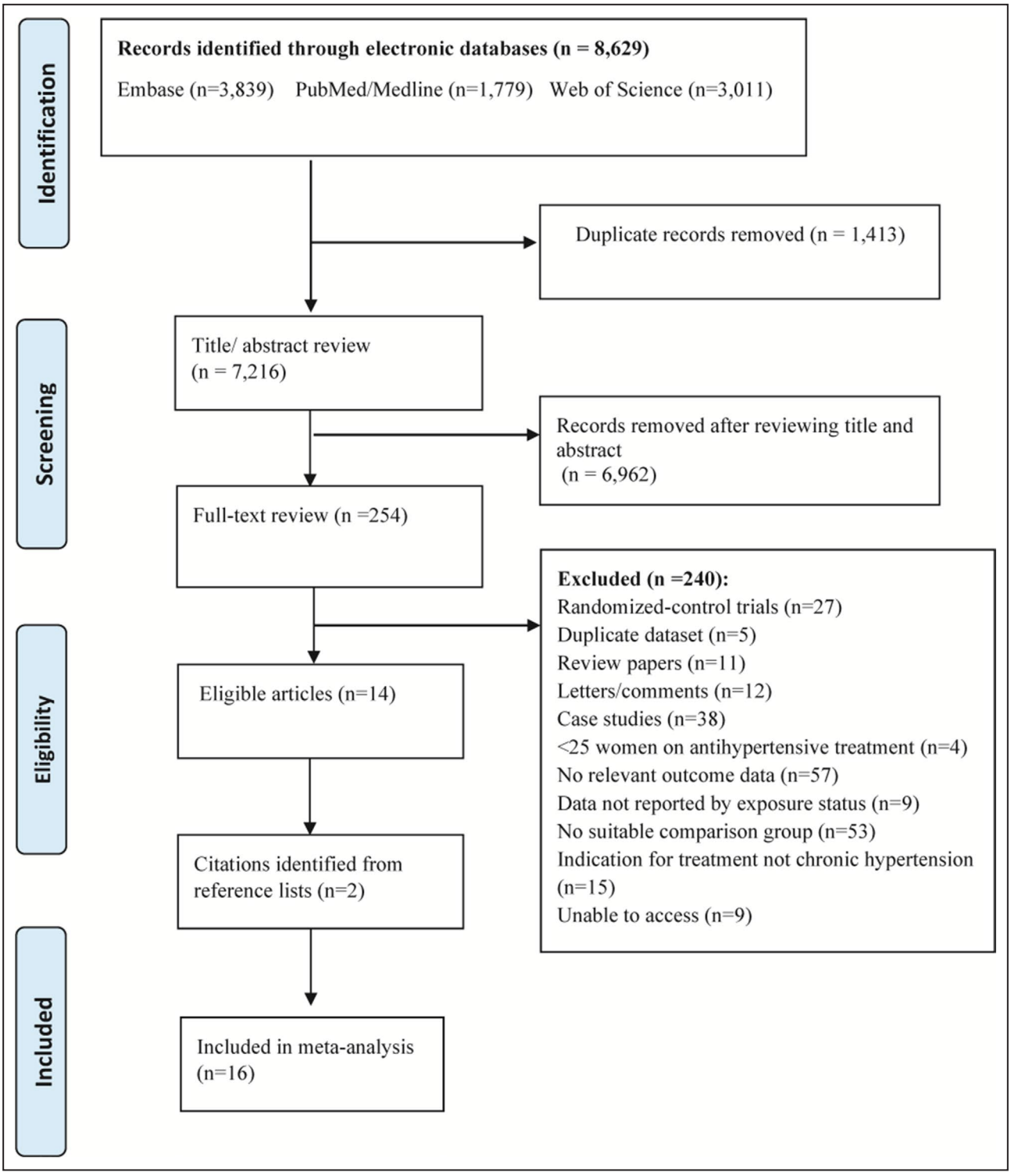


Figure 2. Preferred Reporting Items for Systematic Review and Meta-Analysis flow diagram of studies of antihypertensive treatment during pregnancy.

Black women with chronic hypertension (aOR, 1.84; 95% CI, 1.28–2.65) and White women with chronic hypertension (aOR, 1.64; 95% CI, 1.29–2.07) were higher when compared with their normotensive counterparts. Similar results were found for stillbirth, LBW, and SGA when assessed by maternal race/ethnicity (Table 1; Figures S15 through S18). Yet, the test for subgroup differences indicated that maternal race/ethnicity does not significantly modify the effect of chronic hypertension for PTB (P=0.59),

Table 1. Estimated ORs of Adverse Perinatal Outcome for Women With Chronic Hypertension During Pregnancy Compared With Normotensive Women

Maternal Outcomes	No. of Studies (Estimates)	Population	Overall Crude OR (95% CI)	I^2, %	No. of Studies (Estimates)	Population	Overall Adjusted OR (95% CI)*	I^2, %
Preeclampsia	18	11 721 514	7.11 (5.01–10.09)	100	21	24 312 773	5.43 (3.85–7.65)	100
HELLP syndrome	3	4 744 404	3.60 (2.36–5.50)	73	3	4 744 404	3.08 (1.79–5.30)	81
CS	17 (19)	6 232 257	2.30 (2.02–2.63)	95	9 (10)	18 701 513	1.87 (1.61–2.16)	98
PPH	6	5 786 367	1.57 (1.23–2.00)	85	4	5 446 006	1.46 (1.17–1.81)	72
Maternal mortality	3	39 725 224	8.43 (6.17–11.50)	65	4	52 672 224	4.80 (3.04–7.58)	71
Fetal, neonatal outcomes								
Miscarriage	2	110 269	2.48 (1.78–3.45)	0	1	109 932	1.33 (0.90–1.97)	…
Stillbirth	18	38 345 766	3.00 (2.69–3.35)	80	18	51 197 315	2.32 (2.22–2.42)	0
Black women	…		…	…	2	3 283 628	2.27 (2.00–2.58)	0
White women	…		…	…	2	18 357 481	2.92 (1.75–4.88)	85
VPTB <34 wk	9	2 278 003	2.29 (1.47–3.57)	96	6	2 029 558	1.92 (1.09–3.38)	98
PTB <37 wk	28 (35)**	7 930 708**	2.57 (2.22–2.97)**	97**	25 (30)**	18 713 632**	2.23 (1.96–2.53)**	97**
Nonspecified	23 (28)		2.43 (2.10–2.83)	97	20 (22)		2.14 (1.83–2.51)	97
Spontaneous	3		1.32 (0.97–1.79)	75	4		1.44 (0.74–2.80)	97
Medically indicated	4		6.66 (5.85–7.58)	11	4		4.67 (3.55–6.14)	62
PTB <37 wk								
Black women	…		…	…	5	135 917	1.84 (1.28–2.65)	80
White women	…		…	…	4	155 729	1.64 (1.29–2.07)	95
SGA	29	8 356 964	1.99 (1.58–2.52)	98	24	21 251 640	1.96 (1.61–2.40)	99
Black women	…		…	…	2	16 867	1.30 (1.11–1.54)	0
White women	…		…	…	2	33 673	1.80 (1.22–2.65)	62
LBW	14	4 725 825	2.92 (2.22–3.84)	98	11	4 605 536	3.05 (2.24–4.15)	98
Black women	…		…	…	5	118 757	2.44 (1.94–3.06)	67
White women	…		…	…	4	130 240	3.06 (2.39–3.91)	85
NICU	7	342 254	2.12 (1.66–2.70)	85	1	35 135	1.37 (1.05–1.79)	…
Neonatal death	4	5 196 085	3.11 (2.35–4.11)	39	4	5 301 824	2.29 (2.02–2.59)	0
Perinatal death	10	3 289 474	2.46 (1.70–3.55)	73	6	3 261 503	1.87 (1.33–2.63)	75

References for included studies in this table: preeclampsia,[3,26–45] HELLP syndrome,[32,46,47] CS†, PPH,[32,42,55,62,73,78] maternal mortality,[3,32,97,98] miscarriage,[43,70] stillbirth‡, stillbirth by maternal race/ethnicity (Black/White women),[93,94] VPTB,[9,34,42,43,49,55,58,59] PTB§, PTB by maternal race/ethnicity,[9,53,56,67,95] SGA‖, SGA by maternal race/ethnicity,[9,95] LBW¶, LBW# by maternal race/ethnicity,[9,56,84–86] NICU,[49,51,55,59,78,80,92] neonatal death,[32, 45, 50, 80, 90] and perinatal death.†† CS indicates cesarean section; HELLP syndrome, hemolysis, elevated liver enzyme levels, and low platelet levels; LBW, low birth weight; NICU, neonatal intensive care unit; OR, odds ratio; PPH, postpartum hemorrhage; PTB, preterm birth; SGA, small for gestational age; and VPTB, very PTB.

*Authors' definitions of adjustment.

**This refers to the overall estimates of preterm birth (<37 weeks).

stillbirth (P=0.35), SGA (P=0.13), and LBW (P=0.18). The results of other sensitivity analyses by location or by year of publication did not change the results materially, but we found an increase in odds of maternal mortality over time among US studies (Supplement, page 84). Although there was a high level of heterogeneity between studies, almost all estimates from forest plots consistently supported associations in the same direction. This suggests that the significant heterogeneity was an artefact of relatively large study sizes and small variance around the study-specific effect estimates[118] (Figures 3 and 4 and Figures S1 through S18).

†References 3, 26, 32, 42, 43, 50, 51, 54, 55, 59, 62, 70, 73, 78, 80, 85, 92, 96.

‡References 3, 32, 34, 43, 45, 50, 55, 59, 72, 80, 85, 90, 91, 93, 94, 99–104.

§References 3, 9, 26, 32, 34, 35, 42, 43, 45, 48–69.

‖References 3, 9, 26, 32, 34, 35, 42, 43, 45, 48–51, 54, 55, 59, 60, 69–83.

¶References 9, 32, 51, 56, 60, 62, 69, 80, 84–89.

#References 9, 32, 51, 56, 60, 62, 69, 80, 84–89.

††References 26,42,45,48–51,62,70,73,91.

Effect of Antihypertensive Treatment

Treated Women With Chronic Hypertension Versus Untreated Normotensive Women

The results of the association between antihypertensive treatment and adverse pregnancy outcomes are shown in Table 2. Pregnant women who were treated with

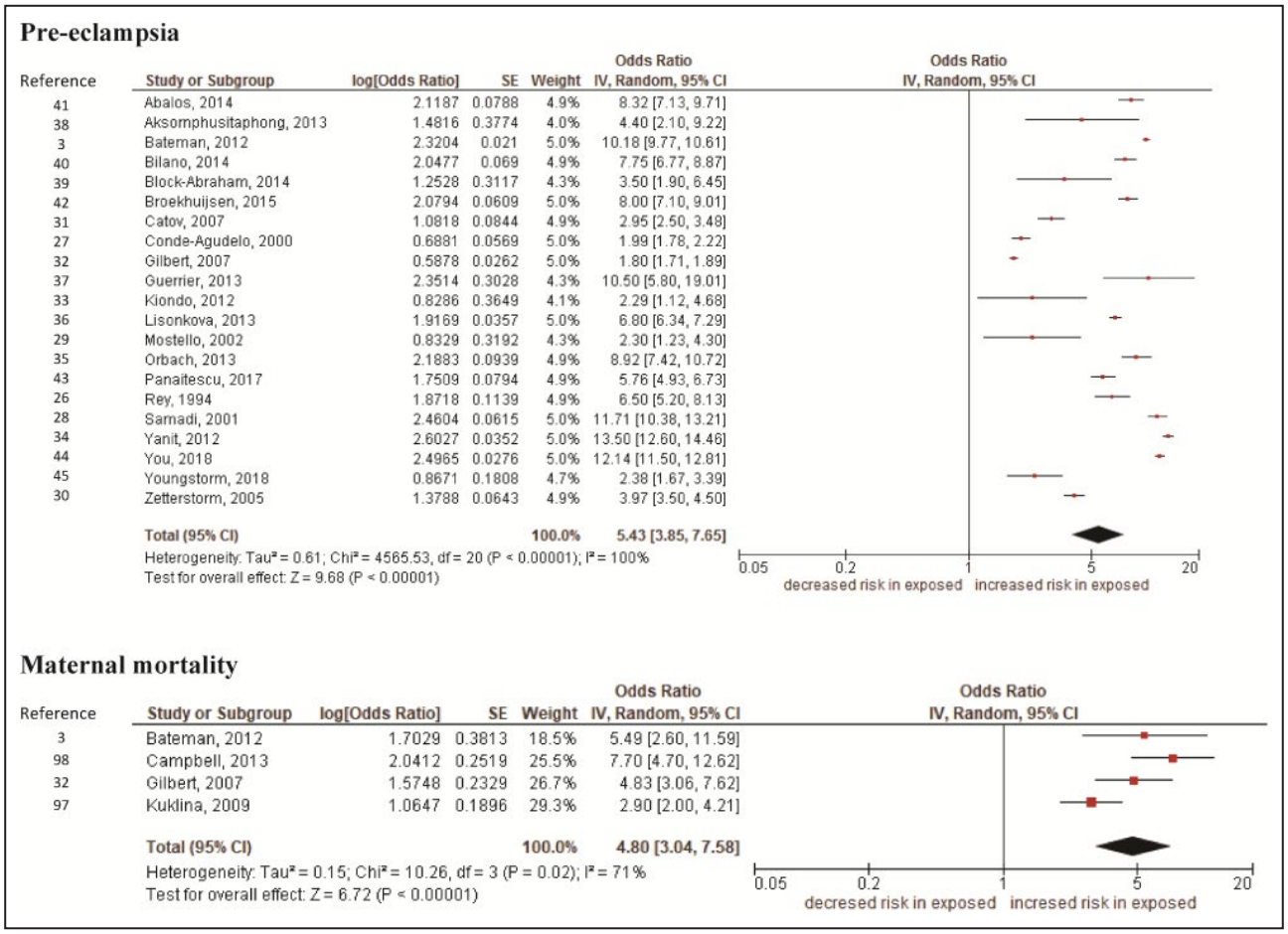


Figure 3. Forest plots of adjusted estimates of the association between chronic hypertension and maternal complications. The red rectangles represent the odd ratio (OR) for each study, and the lateral black lines represent the 95% CI for each study. The diamond represents the overall OR, and the lateral tips of the diamond represent the 95% CI for the combined estimates. IV indicates inverse-variance.

antihypertensive agents had higher odds of preeclampsia (aOR, 6.57; 95% CI, 1.75–24.7); PTB (aOR, 2.78; 95% CI, 1.80–4.29); SGA (aOR, 2.21; 95% CI, 1.18–4.15); LBW (aOR, 3.45; 95% CI, 2.26–5.26); and perinatal death (aOR, 1.80; 95% CI, 1.07–3.01). One study reported the adjusted estimates for the effect of antihypertensive treatment on miscarriage, elective termination of pregnancy, and stillbirth, and showed a nonsignificant association. Heterogeneity was low for stillbirth and perinatal death, but it was moderate to high between studies examining the effect of preeclampsia, PTB, SGA, and LBW. The included studies are large, with precise estimates reflected in tight CIs, which can inflate heterogeneity as overlap between studies' CIs is limited.[21]

Treated Women With Chronic Hypertension Versus Untreated Women With Chronic Hypertension

The data suggested that antihypertensive treatment for women with chronic hypertension did not reduce the risk of adverse perinatal outcomes (Table 2). There were no significant differences in the odds of superimposed preeclampsia (aOR, 0.92; 95% CI, 0.27–3.11) or other adverse outcomes, with the exception of SGA, where the odds were higher for treated women (aOR, 1.86; 95% CI, 1.38–2.50) compared with untreated women. Moreover, there was no strong evidence that the type of antihypertensive treatment influenced the results (Table 3). For women who were on β-blockers only, an association was observed for PTB (aOR, 2.74; 95% CI, 1.40–5.36; 2 studies) and SGA (aOR, 1.84; 95% CI, 1.20–2.82; 3 studies), although these findings were based on a small number of studies. For women who were on a centrally acting antiadrenergic agent only, increased odds were also observed, but were weaker than the effect of β-blockers, for SGA (aOR, 1.62; 95% CI, 1.09–2.42). In addition, one study compared the effect of 2 agents (β-blockers versus methyldopa), and reported an increased risk of SGA in women with chronic hypertension on β-blockers (aOR, 1.95; 95% CI, 1.21–3.15).

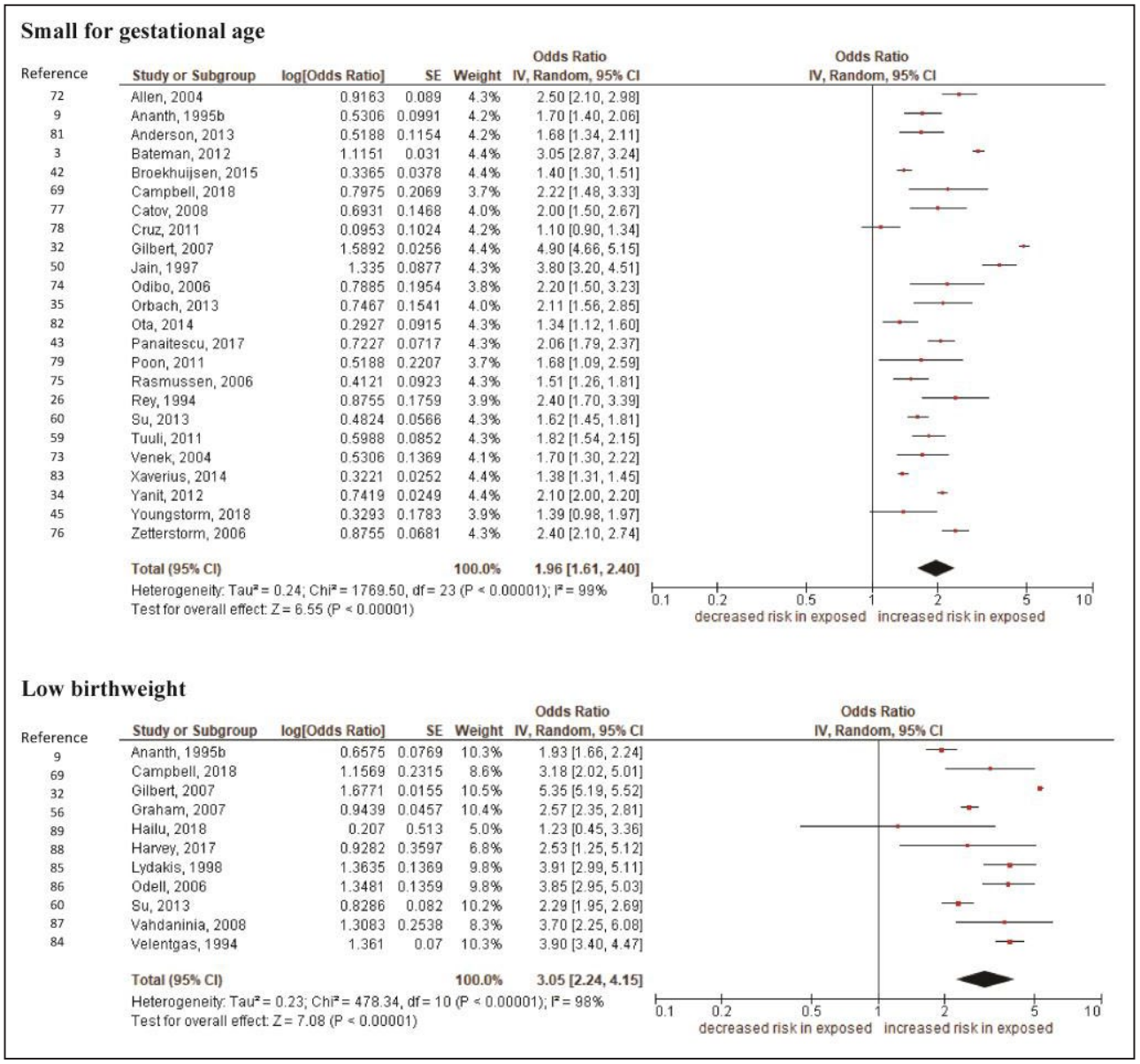


Figure 4. Forest plots of adjusted estimates of the association between chronic hypertension and fetal/neonatal complications.

The red rectangles represent the odd ratio (OR) for each study, and the lateral black lines represent the 95% CI for each study. The diamond represents the overall OR, and the lateral tips of the diamond represent the 95% CI for the combined estimates. IV indicates inverse-variance.

Heterogeneity was observed for most outcomes and may be an artefact of precision of study estimates.[21] However, for preterm birth, estimates varied from OR of 0.44 (95% CI, 0.26–0.74)[111] to OR of 6.25 (95% CI, 4.37–8.94),[109] which warrants caution in the interpretation of the pooled effect (Figure S23B).

DISCUSSION

This comprehensive systematic review and meta-analysis, including 94 studies, examining the effects of maternal chronic hypertension and/or antihypertensive treatment on a broad range of adverse perinatal outcomes demonstrated a significant burden of adverse pregnancy outcomes associated with chronic hypertension. Overall, there was higher odds of maternal, fetal, and neonatal adverse outcomes in women with chronic hypertension, many of which are known to have life-long implications for mothers and their babies, such as increased risks of cardiovascular disease.[119–121] We found no evidence to suggest that the association between chronic hypertension and adverse pregnancy outcomes differs across race/ethnicity.

Table 2. Estimated ORs of Adverse Outcome for Women Treated With Antihypertensive Medications During Pregnancy Compared With Untreated Women

Maternal/Fetal, Neonatal Outcomes	No. of Studies	Population	Overall Crude OR (95% CI)	I^2, %	No. of Studies	Population	Overall Adjusted OR (95% CI)*	I^2, %
Preeclampsia								
Treated CH vs untreated normotensive† [35,45]	2	99 347	8.78 (3.32–23.19)	93	2	99 347	6.57 (1.75–24.7)	96
Treated CH vs untreated CH‡ [109–112,114]	5	1532	0.81 (0.45–1.45)	93	2	641	0.92 (0.27–3.11)	90
Cesarean section								
Treated CH vs untreated normotensive† [107]	1	787	2.26 (1.59–3.22)	…	…	…	…	…
Treated CH vs untreated CH‡ [110]	1	222	1.42 (0.82–2.4)	…	1	222	0.89 (0.58–1.35)	…
Preterm birth (<37 wk)								
Treated CH vs untreated normotensive† [35,45,105–107]	5	1 168 383	2.95 (1.93–4.52)	95	5	1 168 383	2.78 (1.80–4.29)	95
Treated CH vs untreated CH‡ [60,108,110,114]	4	3763	1.35 (0.36–4.97)	97	3	3532	1.88 (0.61–5.74)	97
Small for gestational age								
Treated CH vs untreated normotensive† [35,45,105,117]	4	1 135 723	1.84 (0.79–4.29)	96	4	1 135 723	2.21 (1.18–4.15)	87
Treated CH vs untreated CH‡ [60,108–112]	6	4611	2.21 (1.45–3.35)	76	5	4442	1.86 (1.38–2.50)	53
Low birth weight								
Treated CH vs untreated normotensive† [35,105,106]	3	1 166 502	3.16 (2.03–4.93)	95	3	1 166 502	3.45 (2.26–5.26)	92
Treated CH vs untreated CH‡ [60,114]	2	2958	1.36 (0.63–2.93)	84	1	2727	1.96 (1.44–2.67)	…
Miscarriage								
Treated CH vs untreated normotensive† [107]	1	787	1.61 (0.90–2.88)	…	1	787	1.44 (0.74–2.81)	…
Treated CH vs untreated CH‡ [109]	1	491	0.42 (0.16–1.14)	…	…		…	…
Elective termination of pregnancy								
Treated CH vs untreated normotensive† [107]	1	787	0.24 (0.06–1.00)	…	1	787	0.35 (0.07–1.70)	…
Treated CH vs untreated CH‡ [109]	…							
Stillbirth								
Treated CH vs untreated normotensive† [45,107]	2	1881	2.31 (0.96–5.60)	0	1	1.094	2.20 (0.84–5.76)	…
Treated CH vs untreated CH‡ [109,110]	2	713	1.11 (0.54–2.30)	0	1	222	1.13 (0.32–3.99)	…
Neonatal intensive care unit admission								
Treated CH vs untreated normotensive†	…	…	…	…	…	…	…	
Treated CH vs untreated CH‡ [110,113]	2	271	0.30 (0.17–0.53)	0	1	222	0.43 (0.25–0.74)	…
Perinatal death								
Treated CH vs untreated normotensive† [35,45]	2	99 347	1.77 (1.07–2.93)	0	2	99 347	1.80 (1.07–3.01)	0
Treated CH vs untreated CH‡ [112]	1	169	3.90 (0.43–35.68)	…	…	…	…	…

CH indicates chronic hypertension; and OR, odds ratio.
*Authors' definitions of adjustment.
†The comparative group was untreated normotensive women.
‡All women with CH (treated vs untreated).

Table 3. Estimated ORs of Adverse Outcome for Women, According to Type of Antihypertensive Treatment During Pregnancy

Outcomes	No. of Studies	Population	Overall Crude OR (95% CI)	I^2, %	No. of Studies	Population	Overall Adjusted OR (95% CI)*	I^2, %
PTB <37 wk gestation/exposed to β-blocker agent only								
Treated CH vs untreated normotensive† [35]	1	97 927	2.32 (1.40–3.84)	…	1	97 927	2.68 (1.57–4.57)	…
Treated CH vs untreated CH‡ [60,108]	2	1811	3.00 (1.34–6.72)	84	2	1811	2.74 (1.40–5.36)	77
SGA/exposed to β-blocker agent only								
Treated CH vs untreated normotensive† [35]	1	97 927	3.35 (1.47–7.64)	…	1	97 927	4.80 (2.07–11.1)	…
Treated CH vs untreated CH‡ [60,108,109]	3	2040	2.21 (1.28–3.82)	70	3	2040	1.84 (1.20–2.82)	41
SGA/exposed to centrally acting antiadrenergic agent only								
Treated CH vs untreated normotensive† [35]	1	98 160	1.36 (0.67–2.76)	…	1	98 160	1.01 (1.00–1.02)	…
Treated CH vs untreated CH‡ [60,110,112]	3	1545	1.95 (1.12–3.40)	56	2	1409	1.62 (1.09–2.42)	32
SGA (single/multiple agents vs untreated women with CH‡)								
Single agent[60,108,109]	…	…	…	…	3	2103	2.03 (1.20–3.43)	56
Multiple agents[60,108,109]	…	…	…	…	3	1733	2.55 (1.64–3.95)	30
SGA (centrally acting antiadrenergic vs other agents in women with CH)								
Treated women with CH[35,60,112,115,116]	5	2190	0.82 (0.51–1.32)	61	…	…	…	…
SGA (β-blocker agent vs methyldopa in women with CH)								
Treated women with CH[35,60,115]	3	2126	1.40 (0.70–2.79)	78	1		1.95 (1.21–3.15)	…

CH indicates chronic hypertension; OR, odds ratio; PTB, preterm birth; and SGA, small for gestational age.
*Authors' definitions of adjustment.
†The comparative group was untreated normotensive women.
‡All women with CH (treated vs untreated).

Although antihypertensive treatment might have a potential benefit for mothers, such as preventing severe hypertension and stroke,[122–124] the comparison with normotensive women demonstrated that antihypertensive treatment did not ameliorate the risk of adverse pregnancy outcomes. Moreover, the use of antihypertensive agents for the treatment of chronic hypertension did not reduce the occurrence of adverse perinatal outcomes compared with untreated hypertensive women. Potential differences were observed in the risk of PTB and SGA, depending on the agent, whereas women on multiple antihypertensive agents, likely a reflection of the severity of their hypertension, had increased odds of SGA. These findings warrant further investigation through population-based studies and large randomized trials, such as the 2 ongoing trials of antihypertensive treatment. One trial is examining the effect of nifedipine versus labetalol (Giant PANDA [Pregnancy Antihypertensive Drugs: Which Agent is Best?], NIHR128721), whereas the other one is evaluating whether a blood pressure treatment strategy "only when blood pressure is severe" during pregnancy is effective and safe (CHAP [Chronic Hypertension and Pregnancy], NCT02299414).

Strengths and Limitations of the Study

This review summarized the literature for 14 maternal, fetal, or neonatal outcomes based on predefined rigorous strategies. Moreover, unlike previous reviews, which focused on the effect of either chronic hypertension or antihypertensive treatment, this meta-analysis investigated the impact of both exposures with a special consideration to the comparative groups (ie, untreated normotensive women and untreated women with chronic hypertension). That enabled us to assess if antihypertensive treatment neutralizes the risk of adverse pregnancy outcome among treated women compared with normotensive untreated women. In addition, we were able to compare the effect of different agents among women with chronic hypertension.

As we included observational studies only, potential residual confounding is a concern. Some studies did not adjust for important confounders, such as maternal body mass index, smoking, other chronic diseases, and maternal race/ethnicity. However, we conducted sensitivity analysis for studies that stratified the associations by maternal race/ethnicity to better understand its effect on the adverse outcomes. Selection bias may have been an issue for studies that used data from teratology centers to obtain data about antihypertensive treatment.[107] We cannot eliminate the possibility of misclassification of women with white-coat hypertension as chronic hypertension, which could decrease the magnitude of the pooled estimates. In addition, outcome definitions vary across studies, specifically for superimposed preeclampsia, and this heterogeneity might be a limitation in previous literature.

Adherence to treatment is another limitation in the current literature, as included studies failed to assess the level of adherence. Most of these studies did not report the severity of hypertension nor the gestational age when treatment was initiated. Contamination by superimposed preeclampsia among women with chronic hypertension is another limitation of the literature because these women could potentially lead to an overestimation of the effect. However, the data suggest similar incidences of superimposed preeclampsia among treated (25%) and untreated (22%) women with chronic hypertension.

Comparison With Previous Studies or Reviews

A previous systematic review that assessed the effect of chronic hypertension on pregnancy outcomes concluded that chronic hypertension was associated with high incidence of adverse pregnancy outcomes compared with the US general obstetric population.[12] Our study reinforces these previous findings by including more studies from different settings and analyzing 14 adverse perinatal outcomes between women with chronic hypertension and normotensive women. In contrast to the previous review, we considered different types of PTB, and we found that women with chronic hypertension were ≈5 times more likely to deliver preterm because of an obstetric intervention, which can contribute to the higher risk of neonatal intensive care unit admission and perinatal death. The risk of preeclampsia and hemolysis, elevated liver enzyme levels, and low platelet levels was higher among women with chronic hypertension and may have resulted in higher incidence of medical intervention and preterm delivery.

Previous studies have yielded conflicting results on the modifying effect of maternal race/ethnicity on the association between chronic hypertension and adverse pregnancy outcomes. Some reported increased risk of adverse pregnancy outcomes among Black women,[67,95] others reported no differences,[94,125] whereas some studies reported increased risk among White women.[9,56] Our results suggested that maternal race/ethnicity does not modify the association between chronic hypertension and adverse pregnancy outcomes. Although there was a variation in the pooled estimates of adverse pregnancy outcomes by maternal race/ethnicity, the risk of adverse outcomes was consistently higher in women with chronic hypertension when compared with their normotensive counterparts of the same race/ethnicity.

Although data from RCTs represent the best evidence when examining an intervention such as treatment, previous meta-analyses of RCTs investigating

the effect of using antihypertensive treatment among women with chronic hypertension, compared with no treatment, concluded that treatment decreased their risk of developing severe episodes of hypertension.[122–124] Yet, the effects of antihypertensive treatment on other clinically important outcomes, such as preeclampsia and SGA, remain unclear, possibly because of a lack of statistical power in existing trials, most of which have been of a small scale and with moderate to poor quality, as authors of meta-analyses stated.[122–124]

Moreover, the most recent trial of 894 women by Easterling et al, which compared the effect of 3 antihypertensive agents (labetalol, nifedipine, and methyldopa) for the management of severe hypertension in pregnancy, reported that the 3 oral antihypertensive agents reduced blood pressure to the reference range.[126] On the other hand, more neonates born to women assigned to the nifedipine were admitted to neonatal intensive care unit, whereas the effects of antihypertensive treatment on other obstetric outcomes remained uncertain because of a lack of statistical power. The trial was powered on the basis of blood pressure as the primary outcome and not for neonatal outcomes. Therefore, including only observational studies can be justified because RCTs have been designed and powered to focus mainly on controlling maternal blood pressure rather than comparing adverse maternal and neonatal outcomes. Our findings, therefore, complement previous meta-analyses of RCTs.

A systematic review of 6 trials and 495 hypertensive participants reported that lowering maternal blood pressure to the normal reference range had no significant effect on the risk of SGA or preeclampsia.[124] Similarly, we did not find an association between antihypertensive treatment and preeclampsia. However, the effect of treatment with antihypertensives was consistent with an increased risk of SGA in our review, and this is in agreement with findings from a recent network meta-analysis that reported a higher risk of SGA in women with chronic hypertension who were on β-blockers or methyldopa during pregnancy.[127] This could result from a direct effect of the treatment or because severe hypertension at any time during pregnancy is a risk factor for SGA, and women with severe hypertension are more likely to be treated. Although the CHIPS (Control of Hypertension in Pregnancy Study) found no significant differences in the risk of perinatal mortality and morbidity between less-tight (target diastolic blood pressure, 100 mm Hg) versus tight (target diastolic blood pressure, 85 mm Hg) groups, a higher incidence of severe hypertension was noticed in the less-tight group.[128] Another finding from CHIPS demonstrated that women with severe hypertension (whether in less-tight or tight group) had higher risk of adverse pregnancy outcomes, including SGA.[129] However, 75% of included women in CHIPS had chronic hypertension, whereas the remaining had gestational hypertension.

Perspectives

Pregnancies complicated with chronic hypertension appear to be at increased risk of significant morbidity and mortality. The MBRRACE-UK (Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries) Perinatal Mortality Surveillance Report highlighted the need to reduce stillbirth and adverse outcomes, particularly in Black women, who are disproportionately affected by chronic hypertension.[130] Although rates of maternal mortality have decreased in many countries, the United States was recently listed by the World Health Organization as 1 of the 8 countries with an increasing rate of maternal mortality.[131] In the United Kingdom, <9 mothers per 100 000 live births died from complications related to pregnancy or child birth; in Canada, the rate was <7; whereas in the United States, it increased from 23 in 2005 to 25 in 2015.[131–133] Although our findings (including 4 US studies) suggested an increase in odds of maternal mortality over time among US mothers with chronic hypertension compared with normotensive women, only 2 of 4 studies adjusted for race/ethnicity during the analysis stage (Supplement page 84). Moreover, the Confidential Enquiries Into Maternal Deaths and Morbidity 2014 to 2016 demanded urgent research to investigate why maternal mortality is disproportionately high among Black women and among those with multiple health problems or other vulnerabilities.[130]

Our study supports previous recommendations that women with chronic hypertension should be assessed before conception and monitored closely for the potential development of adverse complications during pregnancy.[134,135] Furthermore, the importance of preconceptual counselling for high-risk women is highlighted by the finding that some hypertensive women were on angiotensin-converting enzyme inhibitors or angiotensin receptor blockers during pregnancy, and these may have teratogenic effects, or result in termination of pregnancy. We found little or no effect of antihypertensive treatment in preventing superimposed preeclampsia, stillbirth, or other adverse perinatal outcomes. Although the lack of data on chronic hypertension severity is an important limitation in the existing literature, our findings should not discourage practitioners from prescribing antihypertensive treatment, when clinically indicated.

Future research should consider severity of hypertension and other confounding factors, such as body

mass index, smoking, and use of antihypertensive treatment, when assessing the association between chronic hypertension and adverse perinatal outcomes. Moreover, population-based studies and large multicenter trials are needed to assess the efficacy and safety of different antihypertensive agents during pregnancy on perinatal outcomes to ensure that healthcare practitioners have sufficient information to determine whether the benefits of treating women with mild-moderate hypertension in pregnancy outweigh potential harms.

CONCLUSIONS

Maternal chronic hypertension is associated with adverse maternal, fetal, and neonatal outcomes, including maternal and perinatal mortality, compared with normotensive women. These associations appear to be independent of maternal race/ethnicity. Treatment with antihypertensive agents did not eliminate the risk of adverse pregnancy outcomes and may increase the risk of SGA. However, various classes of antihypertensive treatment may differently influence the risk of adverse pregnancy outcomes. Further RCTs are needed to examine the effect of antihypertensive treatment on SGA and other adverse pregnancy outcomes.

ARTICLE INFORMATION

Received September 9, 2020; accepted December 29, 2020.

Affiliations

From the School of Public Health (S.Y.A.K., É.J.O., P.M.B., A.S.K.) and INFANT Research Centre (S.Y.A.K., P.M.B., F.P.M., A.S.K.), University College Cork, Ireland; Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA (É.J.O.); Federal University of Pernambuco, Recife, Brazil (D.F.B.L.); Department of Anatomy and Neuroscience (L.C.P.) and Department of Obstetrics and Gynaecology, University College Cork, Cork, Ireland (F.P.M.).

Sources of Funding

This work funded by Ministry of Education, Saudi Arabia (reference No. KSP12021033), in the form of PhD scholarship for S.A. Al Khalaf. The funding agency has no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or approval of the manuscript. Open access funded by grant awarded by HRB Ireland to FMC (SDAP-2019-017).

Disclosures

None.

Supplementary Material

Data S1–S2
Tables S1–S27
Figures S1–S26

REFERENCES

1. Brown MA, Magee LA, Kenny LC, Karumanchi SA, McCarthy FP, Saito S, Hall DR, Warren CE, Adoyi G, Ishaku S. Hypertensive disorders of pregnancy: ISSHP classification, diagnosis, and management recommendations for international practice. *Hypertension*. 2018;72:24–43. DOI: 10.1161/HYPERTENSIONAHA.117.10803.
2. Umesawa M, Kobashi G. Epidemiology of hypertensive disorders in pregnancy: prevalence, risk factors, predictors and prognosis. *Hypertens Res*. 2017;40:213–220. DOI: 10.1038/hr.2016.126.
3. Bateman BT, Bansil P, Hernandez-Diaz S, Mhyre JM, Callaghan WM, Kuklina EV. Prevalence, trends, and outcomes of chronic hypertension: a nationwide sample of delivery admissions. *Am J Obstet Gynecol*. 2012;206:134.e131–134.e138. DOI: 10.1016/j.ajog.2011.10.878.
4. Roberts CL, Bell JC, Ford JB, Hadfield RM, Algert CS, Morris JM. The accuracy of reporting of the hypertensive disorders of pregnancy in population health data. *Hypertens Pregnancy*. 2008;27:285–297. DOI: 10.1080/10641950701826695.
5. American College of Obstetricians Gynecologists. Hypertension in pregnancy: report of the American College of Obstetricians and Gynecologists' Task Force on hypertension in pregnancy. *Obstet Gynecol*. 2013;122:1122–1131. DOI: 10.1097/01.AOG.0000437382.03963.88.
6. Heslehurst N, Rankin J, Wilkinson J, Summerbell CA. Nationally representative study of maternal obesity in England, UK: trends in incidence and demographic inequalities in 619 323 births, 1989–2007. *Int J Obes*. 2010;34:420–428. DOI: 10.1038/ijo.2009.250.
7. Poston L, Caleyachetty R, Cnattingius S, Corvalán C, Uauy R, Herring S, Gillman MW. Preconceptional and maternal obesity: epidemiology and health consequences. *Lancet Diabetes Endocrinol*. 2016;4:1025–1036. DOI: 10.1016/S2213-8587(16)30217-0.
8. Knight M, Kurinczuk JJ, Spark P, Brocklehurst P. Extreme obesity in pregnancy in the United Kingdom. *Obstet Gynecol*. 2010;115:989–997. DOI: 10.1097/AOG.0b013e3181da8f09.
9. Ananth CV, Peedicayil A, Savitz DA. Effect of hypertensive diseases in pregnancy on birthweight, gestational duration, and small-for-gestational-age births. *Epidemiology*. 1995;6:391–395.
10. Matthews TJ, Hamilton BE. Delayed childbearing: more women are having their first child later in life. *NCHS Data Brief*. 2009:1–8.
11. Martin JA, Hamilton BE, Ventura SJ, Osterman MJ, Wilson EC, Mathews T. Births: final data for 2009. *Natl Vital Stat Rep*. 2012;61:1–72.
12. Bramham K, Parnell B, Nelson-Piercy C, Seed PT, Poston L, Chappell LC. Chronic hypertension and pregnancy outcomes: systematic review and meta-analysis. *BMJ*. 2014;348:g2301. DOI: 10.1136/bmj.g2301.
13. Sibai BM. Chronic hypertension in pregnancy. *Obstet Gynecol*. 2002;100:369–377. DOI: 10.1097/00006250-200208000-00029.
14. Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, Himmelfarb CD, DePalma SM, Gidding S, Jamerson KA, Jones DW, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2018;71:e127–e248. DOI: 10.1161/HYP.0000000000000066.
15. National Clinical Guideline Centre (UK). *Hypertension: the clinical management of primary hypertension in adults: update of clinical guidelines 18 and 34*. London, UK: Royal College of Physicians, National Institute for Health and Clinical Excellence: Guidance; 2011.
16. James PR, Nelson-Piercy C. Management of hypertension before, during, and after pregnancy. *Heart*. 2004;90:1499–1504. DOI: 10.1136/hrt.2004.035444.
17. Al Khalaf S, Khashan A, McCarthy F, Barrett P, O'Reilly E.The impact of chronic hypertension and antihypertensive treatment on adverse maternal and perinatal outcomes. PROSPERO 2019 CRD42019120088. Available at: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019120088. Accessed May 17, 2020.
18. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med*. 2009;151:264–269. DOI: 10.7326/0003-4819-151-4-200908180-00135.
19. Zeng X, Zhang Y, Kwong JS, Zhang C, Li S, Sun F, Niu Y, Du L. The methodological quality assessment tools for preclinical and clinical studies, systematic review and meta-analysis, and clinical practice guideline: a systematic review. *J Evid Based Med*. 2015;8:2–10. DOI: 10.1111/jebm.12141.
20. Borenstein M, Hedges LV, Higgins JP, Rothstein HR. A basic introduction to fixed-effect and random-effects models for meta-analysis. *Res Synth Methods*. 2010;1:97–111. DOI: 10.1002/jrsm.12.

21. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7:177–188. DOI: 10.1016/0197-2456(86)90046-2.
22. Deeks JJ, Higgins JP, Altman DG, eds. Chapter 10: analysing data and undertaking meta-analyses. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, . eds. *Cochrane Handbook for Systematic Reviews of Interventions*. Cochrane; 2019:241–284. Available at: https://training.cochrane.org/handbook/current/chapter-10. Accessed July 27, 2020.
23. Duval S, Tweedie R. A nonparametric "trim and fill" method of accounting for publication bias in meta-analysis. *J Am Stat Assoc*. 2000;95:89–98.
24. Lin L, Chu H, Murad MH, Hong C, Qu Z, Cole SR, Chen Y. Empirical comparison of publication bias tests in meta-analysis. *J Gen Intern Med*. 2018;33:1260–1267. DOI: 10.1007/s11606-018-4425-7.
25. *Review Manager (RevMan)*: Version 5.3 [computer program]. Copenhagen, Denmark: The Nordic Cochrane Centre, The Cochrane Collaboration; 2014.
26. Rey E, Couturier A. The prognosis of pregnancy in women with chronic hypertension. *Am J Obstet Gynecol*. 1994;171:410–416. DOI: 10.1016/0002-9378(94)90276-3.
27. Conde-Agudelo A, Belizan JM. Risk factors for pre-eclampsia in a large cohort of Latin American and Caribbean women. *BJOG*. 2000;107:75–83. DOI: 10.1111/j.1471-0528.2000.tb11582.x.
28. Samadi AR, Mayberry RM, Reed JW. Preeclampsia associated with chronic hypertension among African-American and White women. *Ethn Dis*. 2001;11:192–200.
29. Mostello D, Catlin TK, Roman L, Holcomb WL Jr, Leet T. Preeclampsia in the parous woman: who is at risk? *Am J Obstet Gynecol*. 2002;187:425–429. DOI: 10.1067/mob.2002.123608.
30. Zetterstrom K, Lindeberg SN, Haglund B, Hanson U. Maternal complications in women with chronic hypertension: a population-based cohort study. *Acta Obstet Gynecol Scand*. 2005;84:419–424. DOI: 10.1111/j.0001-6349.2005.00508.x.
31. Catov JM, Ness RB, Kip KE, Olsen J. Risk of early or severe preeclampsia related to pre-existing conditions. *Int J Epidemiol*. 2007;36:412–419. DOI: 10.1093/ije/dyl271.
32. Gilbert WM, Young AL, Danielsen B. Pregnancy outcomes in women with chronic hypertension: a population-based study. *J Reprod Med*. 2007;52:1046–1051.
33. Kiondo P, Wamuyu-Maina G, Bimenya GS, Tumwesigye NM, Wandabwa J, Okong P. Risk factors for pre-eclampsia in Mulago Hospital, Kampala, Uganda. *Trop Med Int Health*. 2012;17:480–487. DOI: 10.1111/j.1365-3156.2011.02926.x.
34. Yanit KE, Snowden JM, Cheng YW, Caughey AB. The impact of chronic hypertension and pregestational diabetes on pregnancy outcomes. *Am J Obstet Gynecol*. 2012;207:333.e331–333.e336. DOI: 10.1016/j.ajog.2012.06.066.
35. Orbach H, Matok I, Gorodischer R, Sheiner E, Daniel S, Wiznitzer A, Koren G, Levy A. Hypertension and antihypertensive drugs in pregnancy and perinatal outcomes. *Am J Obstet Gynecol*. 2013;208:301.e301–301.e306. DOI: 10.1016/j.ajog.2012.11.011.
36. Lisonkova S, Joseph KS. Incidence of preeclampsia: risk factors and outcomes associated with early-versus late-onset disease. *Am J Obstet Gynecol*. 2013;209:544.e1–544.e12. DOI: 10.1016/j.ajog.2013.08.019.
37. Guerrier G, Oluyide B, Keramarou M, Grais R. Factors associated with severe preeclampsia and eclampsia in Jahun, Nigeria. *Int J Womens Health*. 2013;5:509–513. DOI: 10.2147/IJWH.S47056.
38. Aksornphusitaphong A, Phupong V. Risk factors of early and late onset pre-eclampsia. *J Obstet Gynaecol Res*. 2013;39:627–631. DOI: 10.1111/j.1447-0756.2012.02010.x.
39. Block-Abraham DM, Turan OM, Doyle LE, Kopelman JN, Atlas RO, Jenkins CB, Blitzer MG, Baschat AA. First-trimester risk factors for preeclampsia development in women initiating aspirin by 16 weeks of gestation. *Obstet Gynecol*. 2014;123:611–617. DOI: 10.1097/AOG.0000000000000118.
40. Bilano VL, Ota E, Ganchimeg T, Mori R, Souza JP. Risk factors of pre-eclampsia/eclampsia and its adverse outcomes in low- and middle-income countries: a WHO secondary analysis. *PLoS One*. 2014;9:e91198. DOI: 10.1371/journal.pone.0091198.
41. Abalos E, Cuesta C, Carroli G, Qureshi Z, Widmer M, Vogel JP,Souza JP. Pre-eclampsia, eclampsia and adverse maternal and perinatal outcomes: a secondary analysis of the World Health Organization Multicountry Survey on Maternal and Newborn Health. *BJOG*. 2014;121(suppl 1):14–24. DOI: 10.1111/1471-0528.12629.
42. Broekhuijsen K, Ravelli AC, Langenveld J, Van Pampus MG, Van den Berg PP, Mol BW, Franssen MT. Maternal and neonatal outcomes of pregnancy in women with chronic hypertension: a retrospective analysis of a national register. *Acta Obstet Gynecol Scand*. 2015;94:1337–1345. DOI: 10.1111/aogs.12757.
43. Panaitescu AM, Syngelaki A, Prodan N, Akolekar R, Nicolaides KH. Chronic hypertension and adverse pregnancy outcome: a cohort study. *Ultrasound Obstet Gynecol*. 2017;50:228–235. DOI: 10.1002/uog.17493.
44. You SH, Cheng PJ, Chung TT, Kuo CF, Wu HM, Chu PH. Population-based trends and risk factors of early- and late-onset preeclampsia in Taiwan 2001–2014. *BMC Pregnancy Childbirth*. 2018;18:199. DOI: 10.1186/s12884-018-1845-7.
45. Youngstrom M, Tita A, Grant J, Szychowski JM, Harper LM. Perinatal outcomes in women with a history of chronic hypertension but normal blood pressures before 20 weeks of gestation. *Obstet Gynecol*. 2018;131:827–834. DOI: 10.1097/AOG.0000000000002574.
46. Fitzpatrick KE, Hinshaw K, Kurinczuk JJ, Knight M. Risk factors, management, and outcomes of hemolysis, elevated liver enzymes, and low platelets syndrome and elevated liver enzymes, low platelets syndrome. *Obstet Gynecol*. 2014;123:618–627. DOI: 10.1097/AOG.0000000000000140.
47. Malmstrom O, Morken NH. HELLP syndrome, risk factors in first and second pregnancy: a population-based cohort study. *Acta Obstet Gynecol Scand*. 2018;97:709–716. DOI: 10.1111/aogs.13322.
48. Acien P, Lloret G, Lloret M. Perinatal morbidity and mortality in pregnancy hypertensive disorders: prognostic value of the clinical and laboratory findings. *Int J Gynaecol Obstet*. 1990;32:229–235. DOI: 10.1016/0020-7292(90)90350-T.
49. McCowan LM, Buist RG, North RA, Gamble G. Perinatal morbidity in chronic hypertension. *Br J Obstet Gynaecol*. 1996;103:123–129. DOI: 10.1111/j.1471-0528.1996.tb09662.x.
50. Jain L. Effect of pregnancy-induced and chronic hypertension on pregnancy outcome. *J Perinatol*. 1997;17:425–427.
51. Hartikainen AL, Aliharmi RH, Rantakallio PT. A cohort study of epidemiological associations and outcomes of pregnancies with hypertensive disorders. *Hypertens Pregnancy*. 1998;17:31–41. DOI: 10.3109/10641959809072236.
52. Meis PJ, Goldenberg RL, Mercer BM, Iams JD, Moawad AH, Miodovnik M, Menard MK, Caritis SN, Thurnau GR, Bottoms SF, et al. The preterm prediction study: risk factors for indicated preterm births. *Am J Obstet Gynecol*. 1998;178:562–567. DOI: 10.1016/S0002-9378(98)70439-9.
53. Samadi AR, Mayberry RM. Maternal hypertension and spontaneous preterm births among black women. *Obstet Gynecol*. 1998;91:899–904. DOI: 10.1016/s0029-7844(98)00087-8.
54. Lydakis C, Beevers M, Beevers DC, Gyh Lip MD. The prevalence of pre-eclampsia and obstetric outcome in pregnancies of normotensive and hypertensive women attending a hospital specialist clinic. *Int J Clin Pract*. 2001;55:361–367.
55. Roberts CL, Algert CS, Morris JM, Ford JB, Henderson-Smart DJ. Hypertensive disorders in pregnancy: a population-based study. *Med J Aust*. 2005;182:332–335. DOI: 10.5694/j.1326-5377.2005.tb06730.x.
56. Graham J, Zhang L, Schwalberg R. Association of maternal chronic disease and negative birth outcomes in a non-Hispanic Black-White Mississippi birth cohort. *Public Health Nurs*. 2007;24:311–317. DOI: 10.1111/j.1525-1446.2007.00639.x.
57. Carter MF, Fowler S, Holden A, Xenakis E, Dudley D. The late preterm birth rate and its association with comorbidities in a population-based study. *Am J Perinatol*. 2011;28:703–707. DOI: 10.1055/s-0031-1280592.
58. Ferrazzani S, Luciano R, Garofalo S, D'Andrea V, De Carolis S, De Carolis MP, Paolucci V, Romagnoli C, Caruso A. Neonatal outcome in hypertensive disorders of pregnancy. *Early Hum Dev*. 2011;87:445–449. DOI: 10.1016/j.earlhumdev.2011.03.005.
59. Tuuli MG, Rampersad R, Stamilio D, Macones G, Odibo AO. Perinatal outcomes in women with preeclampsia and superimposed preeclampsia: do they differ? *Am J Obstet Gynecol*. 2011;204:508.e1–508.e7. DOI: 10.1016/j.ajog.2011.01.065.
60. Su CY, Lin HC, Cheng HC, Yen AM, Chen YH, Kao S. Pregnancy outcomes of anti-hypertensives for women with chronic hypertension: a population-based study. *PLoS One*. 2013;8:e53844. DOI: 10.1371/journal.pone.0053844.
61. Morisaki N, Togoobaatar G, Vogel JP, Souza JP, Rowland Hogue CJ, Jayaratne K, Ota E, Mori R. Risk factors for spontaneous

and provider-initiated preterm delivery in high and low Human Development Index countries: a secondary analysis of the World Health Organization Multicountry Survey on Maternal and Newborn Health. *BJOG*. 2014;121:101–109. DOI: 10.1111/1471-0528.12631.
62. Ye C, Ruan Y, Zou L, Li G, Li C, Chen Y, Jia C, Megson IL, Wei J, Zhang W. The 2011 survey on hypertensive disorders of pregnancy (HDP) in China: prevalence, risk factors, complications, pregnancy and perinatal outcomes. *PLoS One*. 2014;9:e100180. DOI: 10.1371/journal.pone.0100180.
63. Arora CP, Kacerovsky M, Zinner B, Ertl T, Ceausu I, Rusnak I, Shurpyak S, Sandhu M, Hobel CJ, Dumesic DA, et al. Disparities and relative risk ratio of preterm birth in six Central and Eastern European centers. *Croat Med J*. 2015;56:119–127. DOI: 10.3325/cmj.2015.56.119.
64. Derakhshi B, Esmailnasab N, Ghaderi E, Hemmatpour S. Risk factor of preterm labor in the west of Iran: a case-control study. *Iran J Public Health*. 2014;43:499–506.
65. Tucker CM, Berrien K, Menard MK, Herring AH, Daniels J, Rowley DL, Halpern CT. Predicting preterm birth among women screened by North Carolina's pregnancy medical home program. *Matern Child Health J*. 2015;19:2438–2452. DOI: 10.1007/s10995-015-1763-5.
66. Yang Y, He Y, Li Q, Wang Y, Peng Z, Xu J, Ma X. Preconception blood pressure and risk of preterm birth: a large historical cohort study in a Chinese rural population. *Fertil Steril*. 2015;104:124–130. DOI: 10.1016/j.fertnstert.2015.03.024.
67. Premkumar A, Henry DE, Moghadassi M, Nakagawa S, Norton ME. The interaction between maternal race/ethnicity and chronic hypertension on preterm birth. *Am J Obstet Gynecol*. 2016;215:787.e781–787.e788. DOI: 10.1016/j.ajog.2016.08.019.
68. Souza RT, Cecatti JG, Passini R, Tedesco RP, Lajos GJ, Nomura ML, Rehder PM, Dias TZ, Haddad SM, Pacagnella RC, et al. The burden of provider-initiated preterm birth and associated factors: evidence from the Brazilian multicenter study on preterm birth (EMIP). *PLoS One*. 2016;11:e0148244. DOI: 10.1371/journal.pone.0148244.
69. Campbell EE, Gilliland J, Dworatzek PDN, De Vrijer B, Penava D, Seabrook JA. Socioeconomic status and adverse birth outcomes: a population-based Canadian sample. *J Biosoc Sci*. 2018;50:102–113. DOI: 10.1017/S0021932017000062.
70. Sass N, Moron AF, el-Kadre D, Camano L, de Almeida PA. Study of pregnancy with chronic hypertension [in Portuguese]. *Rev Paul Med*. 1990;108:261–266.
71. Haelterman E, Breart G, ParisLlado J, Dramaix M, Tchobroutsky C. Effect of uncomplicated chronic hypertension on the risk of small-for-gestational age birth. *Am J Epidemiol*. 1997;145:689–695. DOI: 10.1093/aje/145.8.689.
72. Allen VM, Joseph KS, Murphy KE, Magee LA, Ohlsson A. The effect of hypertensive disorders in pregnancy on small for gestational age and stillbirth: a population based study. *BMC Pregnancy Childbirth*. 2004;4:17. DOI: 10.1186/1471-2393-4-17.
73. Vanek M, Sheiner E, Levy A, Mazor M. Chronic hypertension and the risk for adverse pregnancy outcome after superimposed pre-eclampsia. *Int J Gynaecol Obstet*. 2004;86:7–11. DOI: 10.1016/j.ijgo.2004.03.006.
74. Odibo AO, Nelson D, Stamilio DM, Sehdev HM, Macones GA. Advanced maternal age is an independent risk factor for intrauterine growth restriction. *Am J Perinatol*. 2006;23:325–328. DOI: 10.1055/s-2006-947164.
75. Rasmussen S, Irgens LM. The effects of smoking and hypertensive disorders on fetal growth. *BMC Pregnancy Childbirth*. 2006;6:16. DOI: 10.1186/1471-2393-6-16.
76. Zetterstrom K, Lindeberg SN, Haglund B, Hanson U. Chronic hypertension as a risk factor for offspring to be born small for gestational age. *Acta Obstet Gynecol Scand*. 2006;85:1046–1050. DOI: 10.1080/00016340500442654.
77. Catov JM, Nohr EA, Olsen J, Ness RB. Chronic hypertension related to risk for preterm and term small for gestational age births. *Obstet Gynecol*. 2008;112:290–296. DOI: 10.1097/AOG.0b013e31817f589b.
78. Cruz MO, Gao WH, Hibbard JU. Obstetrical and perinatal outcomes among women with gestational hypertension, mild preeclampsia, and mild chronic hypertension. *Am J Obstet Gynecol*. 2011;205:9. DOI: 10.1016/j.ajog.2011.06.033.
79. Poon LCY, Karagiannis G, Staboulidou I, Shafiei A, Nicolaides KH. Reference range of birth weight with gestation and first-trimester prediction of small-for-gestation neonates. *Prenat Diagn*. 2011;31:58–65. DOI: 10.1002/pd.2520.
80. Madi JM, Araújo BF, Zatti H, Rombaldi RL, Madi SRC, de Zorzi P, Terres AZ, Varisco BB, Berti IR, Dal Sochio K, et al. Chronic hypertension and pregnancy at a tertiary-care and university hospital. *Hypertens Pregnancy*. 2012;31:350–356. DOI: 10.3109/10641955.2010.525279.
81. Anderson NH, Sadler LC, Stewart AW, Fyfe EM, McCowan LM. Independent risk factors for infants who are small for gestational age by customised birthweight centiles in a multi-ethnic New Zealand population. *Aust N Z J Obstet Gynaecol*. 2013;53:136–142. DOI: 10.1111/ajo.12016.
82. Ota E, Ganchimeg T, Morisaki N, Vogel JP, Pileggi C, Ortiz-Panozo E, Souza JP, Mori R. Risk factors and adverse perinatal outcomes among term and preterm infants born small-for-gestational-age: secondary analyses of the WHO Multi-Country Survey on Maternal and Newborn Health. *PLoS One*. 2014;9:e105155. DOI: 10.1371/journal.pone.0105155.
83. Xaverius PK, Salas J, Woolfolk CL, Leung F, Yuan J, Chang JJ. Predictors of size for gestational age in St. Louis city and county. *Biomed Res Int*. 2014;2014:515827. DOI: 10.1155/2014/515827.
84. Velentgas P, Benga-De E, Williams MA. Chronic hypertension, pregnancy-induced hypertension, and low birthweight. *Epidemiology*. 1994;5:345–348. DOI: 10.1097/00001648-199405000-00015.
85. Lydakis C, Beevers DG, Beevers M, Lip GYH. Obstetric and neonatal outcome following chronic hypertension in pregnancy among different ethnic groups. *QJM*. 1998;91:837–844. DOI: 10.1093/qjmed/91.12.837.
86. Odell CD, Kotelchuck M, Chetty VK, Fowler J, Stubblefield PG, Orejuela M, Jack BW. Maternal hypertension as a risk factor for low birth weight infants: comparison of Haitian and African-American women. *Matern Child Health J*. 2006;10:39–46. DOI: 10.1007/s10995-005-0026-2.
87. Vahdaninia M, Tavafian SS, Montazeri A. Correlates of low birth weight in term pregnancies: a retrospective study from Iran. *BMC Pregnancy Childbirth*. 2008;8:12. DOI: 10.1186/1471-2393-8-12.
88. Harvey EM, Strobino D, Sherrod L, Webb MC, Anderson C, White JA, Atlas R. Community-academic partnership to investigate low birth weight deliveries and improve maternal and infant outcomes at a Baltimore city hospital. *Matern Child Health J*. 2017;21:260–266. DOI: 10.1007/s10995-016-2153-3.
89. Hailu LD, Kebede DL. Determinants of low birth weight among deliveries at a referral hospital in Northern Ethiopia. *Biomed Res Int*. 2018;2018:8169615. DOI: 10.1155/2018/8169615.
90. Zetterstrom K, Lindeberg SN, Haglund B, Hanson U. The association of maternal chronic hypertension with perinatal death in male and female offspring: a record linkage study of 866,188 women. *BJOG*. 2008;115:1436–1442. DOI: 10.1111/j.1471-0528.2008.01844.x.
91. Ahmad AS, Samuelsen SO. Hypertensive disorders in pregnancy and fetal death at different gestational lengths: a population study of 2 121 371 pregnancies. *BJOG*. 2012;119:1521–1528. DOI: 10.1111/j.1471-0528.2012.03460.x.
92. Hjertberg R, Belfrage P, Hanson U. Conservative treatment of mild and moderate hypertension in pregnancy. *Acta Obstet Gynecol Scand*. 1992;71:439–446. DOI: 10.3109/00016349209021092.
93. Ananth CV, Savitz DA, Bowes WA Jr. Hypertensive disorders of pregnancy and stillbirth in North Carolina, 1988 to 1991. *Acta Obstet Gynecol Scand*. 1995;74:788–793. DOI: 10.3109/00016349509021198.
94. Canterino JC, Ananth CV, Smulian J, Harrigan JT, Vintzileos AM. Maternal age and risk of fetal death in singleton gestations: USA, 1995–2000. *J Matern Fetal Neonatal Med*. 2004;15:193–197. DOI: 10.1080/14767050410001668301.
95. Rey E. Preeclampsia and neonatal outcomes in chronic hypertension: comparison between white and black women. *Ethn Dis*. 1997;7:5–11.
96. Janoudi G, Kelly S, Yasseen A, Hamam H, Moretti F, Walker M. Factors associated with increased rates of caesarean section in women of advanced maternal age. *J Obstet Gynaecol Can*. 2015;37:517–526. DOI: 10.1016/S1701-2163(15)30228-0.
97. Kuklina EV, Ayala C, Callaghan WM. Hypertensive disorders and severe obstetric morbidity in the United States. *Obstet Gynecol*. 2009;113:1299–1306. DOI: 10.1097/AOG.0b013e3181a45b25.
98. Campbell KH, Savitz D, Werner EF, Pettker CM, Goffman D, Chazotte C, Lipkind HS. Maternal morbidity and risk of death at delivery hospitalization. *Obstet Gynecol*. 2013;122:627–633. DOI: 10.1097/AOG.0b013e3182a06f4e.
99. Copper RL, Goldenberg RL, DuBard MB, Davis RO. Risk factors for fetal death in white, black and Hispanic women. *Obstet Gynecol*. 1994;84:490–495.

100. Conde-Agudelo A, Belizan JM, Diaz-Rossello JL. Epidemiology of fetal death in Latin America. *Acta Obstet Gynecol Scand*. 2000;79:371–378.
101. Aagaard-Tillery KM, Holmgren C, Lacoursiere DY, Houssain S, Bloebaum L, Satterfield R, Branch DW, Varner MW. Factors associated with nonanomalous stillbirths: the Utah Stillbirth Database 1992–2002. *Am J Obstet Gynecol*. 2006;194:849–854. DOI: 10.1016/j.ajog.2005.09.017.
102. Reddy UM, Laughon SK, Sun L, Troendle J, Willinger M, Zhang J. Prepregnancy risk factors for antepartum stillbirth in the United States. *Obstet Gynecol*. 2010;116:1119–1126. DOI: 10.1097/AOG.0b013e3181f903f8.
103. Yerlikaya G, Akolekar R, McPherson K, Syngelaki A, Nicolaides KH. Prediction of stillbirth from maternal demographic and pregnancy characteristics. *Ultrasound Obstet Gynecol*. 2016;48:607–612. DOI: 10.1002/uog.17290.
104. Xiong T, Mu Y, Liang J, Zhu J, Li X, Li J, Liu Z, Qu Y, Wang Y, Mu D. Hypertensive disorders in pregnancy and stillbirth rates: a facility-based study in China. *Bull World Health Organ*. 2018;96:531–539. DOI: 10.2471/BLT.18.208447.
105. Lennestål R, Olausson PO, Källén B. Maternal use of antihypertensive drugs in early pregnancy and delivery outcome, notably the presence of congenital heart defects in the infants. *Eur J Clin Pharmacol*. 2009;65:615–625. DOI: 10.1007/s00228-009-0620-0.
106. Banhidy F, Acs N, Puho EH, Czeizel AE. The efficacy of antihypertensive treatment in pregnant women with chronic and gestational hypertension: a population-based study. *Hypertens Res*. 2010;33:460–466. DOI: 10.1038/hr.2010.17.
107. Hoeltzenbein M, Beck E, Fietz AK, Wernicke J, Zinke S, Kayser A, Padberg S, Weber-Schoendorfer C, Meister R, Schaefer C. Pregnancy outcome after first trimester use of methyldopa: a prospective cohort study. *Hypertension*. 2017;70:201–208. DOI: 10.1161/HYPERTENSIONAHA.117.09110.
108. Ray JG, Vermeulen MJ, Burrows EA, Burrows RF. Use of antihypertension medications in pregnancy and the risk of adverse perinatal outcomes: McMaster Outcome Study of Hypertension In Pregnancy 2 (MOS HIP 2). *BMC Pregnancy Childbirth*. 2001;1:6.
109. Bayliss H, Churchill D, Beevers M, Beevers DG. Anti-hypertensive drugs in pregnancy and fetal growth: evidence for "pharmacological programming" in the first trimester? *Hypertens Pregnancy*. 2002;21:161–174. DOI: 10.1081/PRG-120013785.
110. Rezk M, Ellakwa H, Gamal A, Emara M. Maternal and fetal morbidity following discontinuation of antihypertensive drugs in mild to moderate chronic hypertension: a 4-year observational study. *Pregnancy Hypertens*. 2016;6:291–294. DOI: 10.1016/j.preghy.2016.05.002.
111. Nzelu D, Dumitrascu-Biris D, Nicolaides KH, Kametas NA. Chronic hypertension: first-trimester blood pressure control and likelihood of severe hypertension, preeclampsia, and small for gestational age. *Am J Obstet Gynecol*. 2018;218:337.e331–337.e337.
112. Mabie WC, Pernoll ML, Biswas MK. Chronic hypertension in pregnancy. *Obstet Gynecol*. 1986;67:197–205. DOI: 10.1097/00006250-198602000-00008.
113. Helou A, Walker S, Stewart K, George J. Management of pregnancies complicated by hypertensive disorders of pregnancy: could we do better? *Aust N Z J Obstet Gynaecol*. 2017;57:253–259. DOI: 10.1111/ajo.12499.
114. Mito A, Murashima A, Wada Y, Miyasato-Isoda M, Kamiya CA, Waguri M, Yoshimatsu J, Yakuwa N, Watanabe O, Suzuki T, et al. Safety of amlodipine in early pregnancy. *J Am Heart Assoc*. 2019;8:e012093. DOI: 10.1161/JAHA.119.012093.
115. Xie RH, Guo Y, Krewski D, Mattison D, Walker MC, Nerenberg K, Wen SW. Beta-blockers increase the risk of being born small for gestational age or of being institutionalised during infancy. *BJOG*. 2014;121:1090–1096. DOI: 10.1111/1471-0528.12678.
116. Ahmed B, Tran DT, Zoega H, Kennedy SE, Jorm LR, Havard A. Maternal and perinatal outcomes associated with the use of renin-angiotensin system (RAS) blockers for chronic hypertension in early pregnancy. *Pregnancy Hypertens*. 2018;14:156–161. DOI: 10.1016/j.preghy.2018.09.010.
117. Fisher SC, Van Zutphen AR, Werler MM, Romitti PA, Cunniff C, Browne ML. Maternal antihypertensive medication use and selected birth defects in the National Birth Defects Prevention Study. *Birth Defects Res*. 2018;110:1433–1442. DOI: 10.1002/bdr2.1372.
118. Fletcher J. What is heterogeneity and is it important? *BMJ*. 2007;334:94–96. DOI: 10.1136/bmj.39057.406644.68.
119. Wilson BJ, Watson MS, Prescott GJ, Sunderland S, Campbell DM, Hannaford P, Smith WC. Hypertensive diseases of pregnancy and risk of hypertension and stroke in later life: results from cohort study. *BMJ*. 2003;326:845. DOI: 10.1136/bmj.326.7394.845.
120. Palmsten K, Buka SL, Michels KB. Maternal pregnancy-related hypertension and risk for hypertension in offspring later in life. *Obstet Gynecol*. 2010;116:858–864. DOI: 10.1097/AOG.0b013e3181f3a1f9.
121. Phillips DI, Walker BR, Reynolds RM, Flanagan DE, Wood PJ, Osmond C, Barker DJ, Whorwood CB. Low birth weight predicts elevated plasma cortisol concentrations in adults from 3 populations. *Hypertension*. 2000;35:1301–1306. DOI: 10.1161/01.HYP.35.6.1301.
122. Webster LM, Conti-Ramsden F, Seed PT, Webb AJ, Nelson-Piercy C, Chappell LC. Impact of antihypertensive treatment on maternal and perinatal outcomes in pregnancy complicated by chronic hypertension: a systematic review and meta-analysis. *J Am Heart Assoc*. 2017;6:e005526. DOI: 10.1161/JAHA.117.005526.
123. Abalos E, Duley L, Steyn DW, Gialdini C. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. *Cochrane Database Syst Rev*. 2018;10:CD002252. DOI: 10.1002/14651858.CD002252.pub4.
124. Panaitescu AM, Roberge S, Nicolaides KH. Chronic hypertension: effect of blood pressure control on pregnancy outcome. *J Matern Fetal Neonatal Med*. 2019;32:857–863. DOI: 10.1080/14767058.2017.1390742.
125. Sibai BM, Lindheimer M, Hauth J, Caritis S, VanDorsten P, Klebanoff M, MacPherson C, Landon M, Miodovnik M, Paul R, et al. Risk factors for preeclampsia, abruptio placentae, and adverse neonatal outcomes among women with chronic hypertension. *N Engl J Med*. 1998;339:667–671. DOI: 10.1056/NEJM199809033391004.
126. Easterling T, Mundle S, Bracken H, Parvekar S, Mool S, Magee LA, von Dadelszen P, Shochet T, Winikoff B. Oral antihypertensive regimens (nifedipine retard, labetalol, and methyldopa) for management of severe hypertension in pregnancy: an open-label, randomised controlled trial. *Lancet*. 2019;394:1011–1021. DOI: 10.1016/S0140-6736(19)31282-6.
127. Bellos I, Pergialiotis V, Papapanagiotou A, Loutradis D, Daskalakis G. Comparative efficacy and safety of oral antihypertensive agents in pregnant women with chronic hypertension: a network meta-analysis. *Am J Obstet Gynecol*. 2020;223:525–537. DOI: 10.1016/j.ajog.2020.03.016.
128. Magee LA, von Dadelszen P, Rey E, Ross S, Asztalos E, Murphy KE, Menzies J, Sanchez J, Singer J, Gafni A, et al. Less-tight versus tight control of hypertension in pregnancy. *N Engl J Med*. 2015;372:407–417. DOI: 10.1056/NEJMoa1404595.
129. Magee LA, von Dadelszen P, Singer J, Lee T, Rey E, Ross S, Asztalos E, Murphy KE, Menzies J, Sanchez J, et al. The CHIPS Randomized Controlled Trial (Control of Hypertension in Pregnancy Study): is severe hypertension just an elevated blood pressure? *Hypertension*. 2016;68:1153–1159. DOI: 10.1161/HYPERTENSIONAHA.116.07862.
130. Knight MBK, Tuffnell D, Jayakody H, Shakespeare J, Kotnis R, Kenyon S, Kurinczuk JJ, eds., on behalf of MBRRACE-UK. *Saving lives, improving mothers' care - lessons learned to inform maternity care from the UK and Ireland Confidential Enquiries Into Maternal Deaths and Morbidity 2014–16*. Oxford, UK: National Perinatal Epidemiology Unit, University of Oxford; 2018.
131. World Health Organization. *Trends in Maternal Mortality: 1990–2015: Estimates From WHO, UNICEF, UNFPA, World Bank Group and the United Nations Population Division: Executive Summary*. Geneva, Switzerland: World Health Organization; 2015.
132. Creanga AA, Berg CJ, Syverson C, Seed K, Bruce FC, Callaghan WM. Pregnancy-related mortality in the United States, 2006–2010. *Obstet Gynecol*. 2015;125:5–12. DOI: 10.1097/AOG.0000000000000564.
133. Creanga AA, Syverson C, Seed K, Callaghan WM. Pregnancy-related mortality in the United States, 2011–2013. *Obstet Gynecol*. 2017;130:366–373. DOI: 10.1097/AOG.0000000000002114.
134. Webster K, Fishburn S, Maresh M, Findlay SC, Chappell LC. Diagnosis and management of hypertension in pregnancy: summary of updated NICE guidance. *BMJ*. 2019;366:l5119. DOI: 10.1136/bmj.l5119.
135. American College of Obstetricians and Gynecologists. ACOG practice bulletin no. 203: chronic hypertension in pregnancy. *Obstet Gynecol*. 2019;133:e26–e50. DOI: 10.1097/AOG.0000000000003020.

SUPPLEMENTAL MATERIAL

Supplemental Methods (Data S1)

1. Search Strategy for the association between chronic hypertension and adverse perinatal outcomes

A) Search strategy for Web of Science

1. Pregnancy outcome* or obstetric outcome* or birth outcome* or pregnancy complication* or gestational complication*/or obstetric complication/ or birth complication* or labor complication* or uterine complication* or normal birth* or live birth* or pre-term deliver* or preterm deliver* or pre-term birth*or preterm birth* or preterm labor* or pre-term labor* or premature deliver* or premature birth* or premature labor* or prematurity or cesarean* or cesarean section* or csection* or c section* or spontaneous abortion* or miscarriage* or miscarry or stillbirth* or still birth* or intrauterine death* or intra-uterine death* or fetal death* or fetal mortality or neonatal mortalit* or neonatal death* or neo-natal death or neo-natal mortalit* or newborn death* or newborn mortalit* or new born death* or new born mortalit* or perinatal mortalit* or perinatal death* or infant mortalit* or infant death* or postneonatal mortalit* or post-neonatal mortalit* or postneonatal death* or post-neonatal death* or preeclampsia or pre eclampsia or preeclamptic or pre eclamptic or preeclamptic or pre-eclamptic toxemia* or preeclamptic toxemia* or PET or pregnancy toxemia* or toxemia* or EPH toxemia* or EPH gestosis or hypertension-edema-proteinuria gestosis or hypertension edema proteinuria gestosis/ or proteinuria-edemahypertension gestosis/ or proteinuria edema hypertension gestosis or edema proteinuria hypertension gestosis or edema-proteinuria-hypertension gestosis/ or eclampsia/ or eclamptic or HELLP or hemolysis elevated liver enzymes low platelet count/ or hemolysis-elevated liver enzymes-low platelet count or antenatal hemorrage* or antepartum hemorrage* or postnatal hemorrage* or postpartum hemorrage* or postpartum complication* or postnatal complication* or post birth complication* or post labor complication* or maternal outcome* or maternal complication* or fetal outcome* or fetal complication* or neonate complication* or neonatal complication*or newborn complication*/ or gestational age/ or special care baby unit admission* or SCBU admission* or NICU admission* or neonatal intensive care unit admission* or small for gestational age* or SGA* or IUGR* or intrauterine growth restriction* or LBW*or low birth weight* or VLBW* or very low birth weight* or neonatal intraventricular hemorrhage*or Intraventricular hemorrhage of newborn*

2. Essential hypertensi* or chronic hypertensi* or chronic hypertension in pregnanc*

3. Search 1 and 2 were then combined (1 ‘AND’ 2)

B) Search strategy for Embase (via OVID)

1. ('pregnancy outcome' OR 'pregnancy complications' OR 'high risk pregnancy' OR 'labor' OR 'delivery' OR 'fetus outcome' OR 'live birth' OR 'premature labor' OR 'immature and premature labor' OR 'prematurity' OR 'cesarean section' OR 'spontaneous abortion' OR 'stillbirth' OR 'fetus death' OR 'infant mortality' OR 'fetus mortality' OR 'maternal mortality' OR 'perinatal mortality' OR 'preeclampsia' OR 'eclampsia' OR 'eclampsia and preeclampsia' OR 'hellp' OR 'disseminated intravascular coagulation' OR 'magnesium sulfate' OR 'newborn death' OR 'gestational age' OR 'infant low birth weight' OR 'low birth weight' OR 'very low birth weight' OR 'extremely low birth weight' OR 'apgar score' OR 'newborn intensive care' OR 'small for date infant' OR 'pregnancy outcome*' OR 'maternal outcome*' OR 'pregnancy complication*' OR 'obstetric

outcome*' OR 'obstetric complication*' OR 'normal birth*' OR 'live birth*' OR 'premature birth*' OR 'preterm birth*' OR 'preterm deliver*' OR 'born preterm' OR 'cesarean*' OR 'csection*' OR 'miscarriage*' OR 'stillbirth*' OR 'intrauterine death*' OR 'antenatal hemorrhage*' OR 'antenatal haemorrhage*' OR 'antepartum haemorrhage*' OR 'antepartum hemorrhage*' OR 'postpartum hemorrhage*' OR 'postpartum haemorrhage*' OR 'postnatal haemorrhage*' OR 'postnatal hemorrhage*' OR 'postpartum complication*' OR 'postnatal complication*' OR 'special care baby unit admission*' OR 'scbu admission*' OR 'neonatal intensive care unit admission*' OR 'nicu admission*' OR 'sga' OR 'iugr' OR 'neonatal intraventricular haemorrhage' OR 'neonatal intraventricular hemorrhage' OR 'lbw' OR 'vlbw' OR 'fetus outcome*' OR 'high risk pregnan*')

2. Essential hypertensi*/ or chronic hypertensi*/ or chronic hypertension in pregnan*

3. Search 1 and 2 were then combined (1 'AND' 2)

C) Search strategy for Medline (via OVID platform)

1. pregnancy outcome* or pregnancy complication* obstetric complication* or obstetric labor complications/ or pregnancy, high-risk/ or delivery, obstetric or labor or live birth or obstetric labor, premature or premature birth or premature birth* or preterm birth* preterm deliver* or born preterm or caesarean section cesarean* or c-section or caesarean* or abortion, spontaneous or stillbirth or fetal death/ or infant mortality or maternal mortality or perinatal mortality or pre-eclampsia or eclampsia/ or HELLP/ or gestational age/ or infant, low birth weight/ or pregnancy/or or obstetric outcome* or normal birth* or live birth* or miscarriage* or stillbirth* or intrauterine death* or neonatal death*or antenatal haemorrhage* or postpartum haemorrhage* or antenatal hemorrhage* or postpartum hemorrage* or antepartum hemorrage* or antepartum haemorrhage* or postpartum complication*/ or special care baby unit admission* or SCBU admission* or neonatal intensive care unit admission* or NICU admission* or small for gestationa age or SGA or intrauterine growth restriction or IUGR or neonatal intraventricular hemorrage* or neonatal intraventricular haemorrhage*
2. Essential hypertensi* or chronic hypertensi* or chronic hypertension in pregnan*
   Searches 1 and 2 were then combined (1 'AND' 2)

2. Selection process and eligibility criteria

Two of us (SAK and PB) independently reviewed the titles and abstracts of all articles, studies that clearly not meeting the predefined criteria excluded, then the full text of potentially eligible studies obtained. Following that, both investigators independently screened the full text articles to define the included studies and a third investigator (ASK) resolved any inconsistencies about included or excluded articles between the two investigators. In addition, PRISMA flow chart used to illustrate the process for selecting the included studies with the number of references at each phase of this review.

We included cohort and case control studies in which chronic hypertension reported as an exposure (compared to normotensive women); and the outcomes of interest were adverse maternal, fetal, or neonatal outcomes. We excluded study designs other than observational studies, along with case reports, case series, editorials, reviews, conference abstracts, book chapters and animal/in vitro studies. When two or more studies included the same cohort, we included the one with largest population or with more relevant outcomes. Also, studies with additional comorbidities were also excluded. Moreover, as, pre-eclampsia associated with higher risk of adverse outcomes and this review focusing on the impact of chronic hypertension; we included women with chronic hypertension without superimposed pre-eclampsia, when possible. Additionally, when studies reported results for both groups separately, we used the group without pre-eclampsia as it is one of the outcomes of interest.

3. Data collection process and quality assessment

An electronic standardised data extraction form was developed, and pilot tested on seven studies. One of us (SAK extracted the data for all included studies, and two obstetricians (FMC and DF) extracted the data independently for more than 50% of the included studies to ensure the validity of extracted data. The following details extracted from each study: source of data, authors' name, study design, study period, population characteristics (sample size, appropriateness of case and control recruitment, inclusion/exclusion criteria, and definition of exposure, measures, and definitions of outcomes (maternal, fetal and neonatal), appropriateness of analyses, confounders adjusted for (if any), crude and adjusted estimates. Any disagreement about the extracted data was resolved by the third investigator (ASK).

We used the Newcastle-Ottawa Scale (NOS) to assess the study quality. The NOS has a version for case-control studies and one for cohort studies, and it uses a 'star system', in which stars are assigned to show higher quality based on three criteria: selection of the study groups; comparability of the groups; and the ascertainment of the exposure and/or outcome of interest. The quality assessment was assessed independently by two investigators (SAK) and (LP). Any inconsistency between the two investigators resolved by a third investigator (ASK)

Supplemental Methods (Data S2)

1. Search Strategy for the association between antihypertensive treatment and adverse perinatal outcomes

A) Search strategy for Web of Science

1. Anti hypertensive agent*/ or / Antihypertensive agent* Anti-hypertensive agent* / or /Cardiovascular Agent*/ or /anti-hypertensive drug*/ or /antihypertensive drug*/ or /antihypertensive/ or /anti hypertensive drug*/ or /antihypertensive agents therap*/ or /anti hypertensive agents therap*/ or/ anti-hypertensive agents therap*/ or /antihypertensive agents pharmacol*/ or /anti hypertensive agents pharmacol*/ or / anti-hypertensive agents pharmacol*/ or / calcium channel blocker/ OR /beta blocker/ OR /ACEi/ OR /adrenergic receptor antagonist/ or / adrenergic receptor blocker/ OR /alpha-2 adrenergic receptor agonist/ OR /angiotensin ii receptor/ OR /hydralazine/ OR /sodium nitroprusside/ OR /clonidine hydrochloride/ OR /moxonidine/ OR /renin inhibitor/ OR /thiazide/ OR /loop diuretic/ OR /potassium sparing diuretic
2. hypertensi*
3. Pregnancy outcome* or obstetric outcome* or birth outcome* or pregnancy complication* or gestational complication*/or obstetric complication/ or birth complication* or labor complication* or uterine complication* or normal birth* or live birth* or pre-term deliver* or preterm deliver* or pre-term birth*or preterm birth* or preterm labor* or pre-term labor* or premature deliver* or premature birth* or premature labor* or prematurity or cesarean* or cesarean section* or csection* or c section* or spontaneous abortion* or miscarriage* or miscarry or stillbirth* or still birth* or intrauterine death* or intra-uterine death* or fetal death* or fetal mortality or neonatal mortalit* or neonatal death* or neo-natal death or neo-natal mortalit* or newborn death* or newborn mortalit* or new born death* or new born mortalit* or perinatal mortalit* or perinatal death* or infant mortalit* or infant death* or postneonatal mortalit* or post-neonatal mortalit* or postneonatal death* or post-neonatal death* or preeclampsia or pre eclampsia or preeclamptic or pre eclamptic or preeclamptic or pre-eclamptic toxemia* or preeclamptic toxemia* or PET or pregnancy toxemia* or toxemia* or EPH toxemia* or EPH gestosis or hypertension-edema-proteinuria gestosis or hypertension edema proteinuria gestosis/ or proteinuria-edemahypertension gestosis/ or proteinuria edema hypertension gestosis or edema proteinuria hypertension gestosis or edema-proteinuria-hypertension gestosis/ or eclampsia/ or eclamptic or HELLP or hemolysis elevated liver enzymes low platelet count/ or hemolysis-elevated liver enzymes-low platelet count or antenatal hemorrage* or antepartum hemorrage* or postnatal hemorrage* or postpartum hemorrage* or postpartum complication* or postnatal complication* or post birth complication* or post labor complication* or maternal outcome* or maternal complication* or fetal outcome* or fetal complication* or neonate complication* or neonatal complication*or newborn complication*/ or gestational age/ or special care baby unit admission* or SCBU admission* or NICU admission* or neonatal intensive care unit admission* or small for gestational age* or SGA* or IUGR* or intrauterine growth restriction* or LBW*or low birth weight* or VLBW* or very low birth weight* or neonatal intraventricular hemorrhage*or Intraventricular hemorrhage of newborn*
4. Search 1 AND 2 AND 3

B) Search strategy for Embase (via OVID platform)

1. ('pregnancy outcome' OR 'pregnancy complications' OR 'high risk pregnancy' OR 'labor' OR 'delivery' OR 'fetus outcome' OR 'live birth' OR 'premature labor' OR 'immature and premature labor' OR 'prematurity' OR 'cesarean section' OR 'spontaneous abortion' OR 'stillbirth' OR 'fetus death' OR 'infant mortality' OR 'fetus mortality' OR 'maternal mortality' OR 'perinatal mortality' OR 'preeclampsia' OR 'eclampsia' OR 'eclampsia and preeclampsia' OR 'hellp' OR 'disseminated intravascular coagulation' OR 'magnesium sulfate' OR 'newborn death' OR 'gestational age' OR 'infant low

birth weight' OR 'low birth weight' OR 'very low birth weight' OR 'extremely low birth weight' OR 'apgar score' OR 'newborn intensive care' OR 'small for date infant' OR 'pregnancy outcome*' OR 'maternal outcome*' OR 'pregnancy complication*' OR 'obstetric outcome*' OR 'obstetric complication*' OR 'normal birth*' OR 'live birth*' OR 'premature birth*' OR 'preterm birth*' OR 'preterm deliver*' OR 'born preterm' OR 'cesarean*' OR 'csection*' OR 'miscarriage*' OR 'stillbirth*' OR 'intrauterine death*' OR 'antenatal hemorrhage*' OR 'antenatal haemorrhage*' OR 'antepartum haemorrhage*' OR 'antepartum hemorrhage*' OR 'postpartum hemorrhage*' OR 'postpartum haemorrhage*' OR 'postnatal haemorrhage*' OR 'postnatal hemorrhage*' OR 'postpartum complication*' OR 'postnatal complication*' OR 'special care baby unit admission*' OR 'scbu admission*' OR 'neonatal intensive care unit admission*' OR 'nicu admission*' OR 'sga' OR 'iugr' OR 'neonatal intraventricular haemorrhage' OR 'neonatal intraventricular hemorrhage' OR 'lbw' OR 'vlbw' OR 'fetus outcome*' OR 'high risk pregnan*')

2. ('calcium channel blocker' OR 'beta blocker' OR 'acei' OR 'adrenergic receptor antagonist/blocker' OR 'alpha-2 adrenergic receptor agonist' OR 'angiotensin ii receptor' OR 'antihypertensive' OR 'hydralazine' OR 'sodium nitroprusside' OR 'clonidine hydrochloride' OR 'moxonidine' OR 'renin inhibitor' OR 'thiazide' OR 'loop diuretic' OR 'potassium sparing diuretic')
3. Hypertension
4. 1 AND 2 AND 3

C) Search strategy for Medline (via OVID platform)

1. Anti hypertensive agent*/ or / Antihypertensive agent* Anti-hypertensive agent* / or /Cardiovascular Agent*/ or /anti-hypertensive drug*/ or /antihypertensive drug*/ or /antihypertensive/ or /anti hypertensive drug*/ or /antihypertensive agents therap*/ or /anti hypertensive agents therap*/ or/ anti-hypertensive agents therap*/ or /antihypertensive agents pharmacol*/ or /anti hypertensive agents pharmacol*/ or / anti-hypertensive agents pharmacol*/ or / calcium channel blocker/ OR /beta blocker/ OR /ACEi/ OR /adrenergic receptor antagonist/ or / adrenergic receptor blocker/ OR /alpha-2 adrenergic receptor agonist/ OR /angiotensin ii receptor/ OR /hydralazine/ OR / nitroprusside/ OR /clonidine / OR /thiazide/ OR /loop diuretic/ OR /potassium sparing diuretic
2. Hyperten*
3. pregnancy outcome* or pregnancy complication* obstetric complication* or obstetric labor complications/ or pregnancy, high-risk/ or delivery, obstetric or labor or live birth or obstetric labor, premature or premature birth or premature birth* or preterm birth* preterm deliver* or born preterm or caesarean section cesarean* or c-section or caesarean* or abortion, spontaneous or stillbirth or fetal death/ or infant mortality or maternal mortality or perinatal mortality or pre-eclampsia or eclampsia/ or HELLP/ or gestational age/ or infant, low birth weight/ or pregnancy/or or obstetric outcome* or normal birth* or live birth* or miscarriage* or stillbirth* or intrauterine death* or neonatal death*or antenatal haemorrhage* or postpartum haemorrhage* or antenatal hemorrhage* or postpartum hemorrage* or antepartum hemorrage* or antepartum haemorrhage* or postpartum complication*/ or special care baby unit admission* or SCBU admission* or neonatal intensive care unit admission* or NICU admission* or small for gestationa age or SGA or intrauterine growth restriction or IUGR or neonatal intraventricular hemorrage* or neonatal intraventricular haemorrhage*
4. Search 1 AND 2 AND 3

We used similar to the previously mentioned method, but the exposure is antihypertensive treatment, while the comparative groups divided into 1) untreated normotensive women and 2) untreated women with chronic hypertension.

2. Selection process and eligibility criteria

One of us (SAK) reviewed the titles and abstracts of all articles, studies not meeting the including criteria excluded. Then out of 254 articles, two reviewers (SAK and PB) independently reviewed these studies to decide about including studies.

3. Data collection process and quality assessment

Similarly, one investigator (SAK) extracted the data for all included studies (n=16), and second investigator (DF) extracted the data independently for more than 50% of the included studies to ensure the validity of extracted data. The following details extracted from each study: source of data, authors' name, study design, study period, population characteristics (sample size, appropriateness of case and control recruitment, inclusion/exclusion criteria, and definition of exposure (type of antihypertensive agent / dose/ initiation of treatment), types of hypertension being treated, definitions of outcomes (maternal/fetal and neonatal), appropriateness of analyses, confounders adjusted for (if any), crude and adjusted estimates. Moreover, Newcastle-Ottawa Scale (NOS) was used to assess the study quality, and that was done independently by two investigators (SAK) and (LP). Any inconsistency between the two investigators resolved by a third investigator (ASK)

Table S1: Characteristics of studies for pre-eclampsia (PE) outcome

Author, year published	*Country (ies)*	*Design*	*Sample size*	*Study duration*	*Definition of chronic hypertension*	*Definition of outcome*	*Newcastle-Ottawa grade*
Rey, 1994[26]	Canada	Cohort (hospital-based)	20,375 women	1987 to 1991	Blood pressure (BP) >140/90 mm Hg with a diagnosed before pregnancy or hypertension in at least two measurements<20 weeks of pregnancy and/or 6 weeks after delivery	Superimposed PE: increase in SBP or DPB compared with the first trimester of 30 mm Hg and 15 mm Hg, respectively, with the appearance of protein excretion of >300 mg/day in a 24-hour collection, de novo thrombocytopenia, liver enzymes elevation, or coagulation disorders	6
Conde-Agudelo, 2000a[27]	Latin America and the Caribbean*	Cohort (multicountry)	878,680 pregnancies	1985 to 1997	Chronic hypertension diagnosed using ICD-10 codes	DBP≥90 mmHg on two or more consecutive occasions 24 hours apart or a DBP≥10 mmHg on any one occasion plus proteinuria (one 24-hour urine collection with a total protein excretion of > 300 mg or ≥1+ on a urine dipstick) (ICD-10 codes)	7
Samadi, 2001[28]		Case control (national-based)	182687 women	1988 to 1996	Chronic hypertension diagnosed using ICD-9 codes	ICD-9 codes	7
Mostello, 2002[29]	USA	Case control (population-based)	4702 women	1989 to 1997	History of chronic hypertension	NR (outcome includes PE and eclampsia)	7
Zetterstrom, 20053[0]¥	Sweden	Cohort (population-based)	681,515 women	1992 to 1998	BP≥140/90 mmHg diagnosed before pregnancy, or before 20 weeks' gestation using (ICD-9 and ICD-10 codes)	Preeclampsia: DBP≥90 combined with proteinuria > 300 mg/day or ≥1+ on a urine dipstick.	8
Catov, 2007[31]	Denmark	Cohort (national-based)	69007 women	1997 to 2003	Hypertension reported before pregnancy or at the first interview (16weeks), and/or	BP >140/90mmHg on at least three occasions) in combination with proteinuria of ≥300 mg/l.	8

					reported taking antihypertensive medication		
Gilbert, 2007[32]	USA	Cohort (population-based)	4,324,902 pregnancies	1991 to 2001	Chronic hypertension diagnosed using ICD-9 codes	ICD-9 codes	8
Kiondo, 2012[33]	Uganda	Case control (hospital-based)	559 women	2008 to 2009	History of chronic hypertension before pregnancy or at booking	BP≥160/110 mmHg or two measurements of ≥140/90 mmHg with one 24-hour urine collection with a total protein excretion of > 300 mg or ≥1+ on a urine dipstick	6
Bateman, 2012[3]	USA	Cohort (population-based)	12,947,000	2007 to 2008	Chronic hypertension was defined as hypertension without comorbidities using ICD-9 codes	PE diagnosed using ICD-9 codes	8
Yanit, 2012[34]	USA	Cohort (population-based)	527,937 mother-infant pairs	2006	Chronic hypertension diagnosed using ICD-9 codes	PE diagnosed using ICD-9 codes	8
Orbach, 2013[35‡]	Israel	Cohort (population-based)	100,029 births	1998 to 2008	Chronic hypertension diagnosed using ICD-9 codes	PE diagnosed using ICD-9 codes	8
Lisonkova, 2013[36]	USA	Cohort (population-based)	456,668 mother-infant pairs	2003 to 2008	Chronic hypertension diagnosed using ICD-9 codes	PE diagnosed using ICD-9 codes	8
Guerrier, 2013[37]	Nigeria	Case control (hospital-based)	1676 women	2010 to 2011	History of chronic hypertension	Preeclampsia was defined as new hypertension with BP≥160/110 after 20 weeks of gestation in a woman who was normotensive before 20 weeks gestation, associated with proteinuria (≥2+ on a urine dipstick). Eclampsia was defined as occurrence of seizure and/or altered level of consciousness not caused by epilepsy or other convulsive disorders, with signs of severe preeclampsia.	6

Aksornphusitaphong, 2013[38]	Thailand	Case control (hospital-based)	898 women	2005 to 2010	History of chronic hypertension	Superimposed preeclampsia was defined as a new onset of proteinuria of at least 300 mg/24 h in hypertensive women but no proteinuria prior to 20 weeks' gestation, or a sudden increase in proteinuria or blood pressure in women with hypertension and proteinuria before 20 weeks' gestation.	6
Block-Abraham, 2014[39]	USA	Cohort (hospital-based)	614 women	2007 to 2010	hypertension as SBP>140 mm Hg or DBP>90 mm Hg or both	new-onset or worsening proteinuria and maternal systolic blood pressure 140 mm Hg or greater or diastolic blood pressure 90 mm Hg or greater on two separate occasions, 6 or more hours apart, after 20 weeks of gestation. Preeclampsia superimposed on chronic hypertension was defined as worsening blood pressure and increasing proteinuria after 20 weeks of gestation	6
Bilano, 2014[40]	23 countries**	Cohort (International, multicountry)	276,103 women	(2004 to 2005 in Africa and Latin America), and (between 2007 to 2008 in Asia)	Hypertension diagnosed before pregnancy, or before 20 weeks' gestation	high blood pressure (≥140 mmHg systolic or ≥90 mmHg diastolic or increases of 30 mmHg systolic or 15 mmHg diastolic from the baseline on at least two occasions six or more hours apart) that develops from the 20th, and proteinuria.	7
Abalos, 2014[41]	29 countries***	Cohort (International, multicountry)	312,115 pregnancies	2004 to 2008	BP >140/90 mmHg diagnosed before pregnancy, or before 20 weeks' gestation	presence of hypertension (blood pressure >140/90 mmHg) associated with proteinuria	6
Broekhuijsen, 2015[42]	Netherlands	Cohort (population-based)	988,389 mother-infant pairs	2002 to 2007	BP ≥140/90 mmHg diagnosed before pregnancy, or before 20 weeks' gestation	Preeclampsia is defined as at least one diastolic blood pressure measurement of at least 90mmHg combined with proteinuria of at least 300 mg/day	8

						or 1þ on a urine dipstick. Mild preeclampsia is defined as a diastolic blood pressure from 90 to 109mmHg combined with proteinuria of <500mg/day or 1þ or 2þ on a urine dipstick. Severe preeclampsia is defined as preeclampsia with either a diastolic blood pressure of at least 110mmHg or albuminuria of at least 500mg/day or both	
Panaitescu, 2017[43]	UK	Cohort (hospital-based)	109,932 pregnancies	March 2006 and July 2015/ February 2007 and November 2015	History of chronic hypertension	Superimposed on PE was diagnosed according to the guidelines of the ISSHP: as development of significant proteinuria after 20 weeks' gestation in a previously non-proteinuric woman	8
You S-H, 2018[44]	Taiwan	Cohort (population-based)	2,884,347	2001 to 2014	Chronic hypertension was diagnosed using (ICD-9 codes)	Two occasions of ≥ 140/90 mmHg after 20 weeks of gestation accompanied by proteinuria > 300 mg/day or ≥1+ on dipstick based (using ICD-9 codes)	8
Youngstrom, 2018[45‡]	USA	Cohort (hospital-based)	1,306 mother-infant pairs	2000 to 2014	History of hypertension **or** the use of antihypertensive medication before pregnancy	BP ≥140/90 with either proteinuria (protein excretion ≥300 mg in 24 hours or protein-to-creatinine ratio≥0.3), thrombocytopenia (less than 100,000/mL), transaminases (aspartate aminotransferase > twice the upper limit of normal), or elevated creatinine≥1.2 mg/dL	8

* Uruguay, Argentina, Peru, Colombia, Honduras, Paraguay, Salvador, Chile , Bolivia, Costa Rica, Panama, Dominican Republic, Nicaragua, Brazil, Ecuador, Mexico, Bahamas, and Venezuela

**23 countries; Algeria, Angola, Democratic Republic of Congo, Niger, Nigeria, Kenya, and Uganda from Africa; Argentina, Brazil, Cuba, Ecuador, Mexico, Nicaragua, Paraguay, and Peru from Latin America; and Cambodia, China, India, Nepal, Philippines, Sri Lanka, Thailand, and Vietnam from Asia

***29 countries, African Region (Angola, DR Congo, Kenya, Niger, Nigeria and Uganda); Region of the Americas (Argentina, Brazil, Ecuador, Mexico, Nicaragua, Paraguay and Peru); Eastern Mediterranean Region (Afghanistan, Jordan, Lebanon, occupied Palestinian territory, Palestine, Pakistan and Qatar); South-East Asia Region (India, Nepal, Sri Lanka and Thailand); Western Pacific Region (Cambodia, China, Japan, Mongolia, Philippines and Vietnam)

¥ We combined the odds ratios for mild and severe pre-eclampsia

‡ The odds ratios (ORs) from these studies were combined for treated and untreated women with chronic hypertension.

Table S2: Characteristics of studies for hemolysis, elevated liver enzyme levels, and low platelet levels (HEELP) syndrome outcome

Author, year published	*Country*	*Design*	*Sample size*	*Study duration*	*Definition of chronic hypertension*	*Definition of outcome*	*Newcastle-Ottawa grade*
Gilbert, 2007[32]	USA	Cohort (population-based)	4,324,902 pregnancies	1991 to 2001	Chronic hypertension diagnosed using ICD-9 codes	HELLP syndrome diagnosed using ICD-9 codes	8
Fitzpatrick, 2014[46]	UK	Case-control (national-based	605 women	2011-2012	NR	Elevated liver enzymes: (Serum aspartate aminotransferase ≥70 international units/L OR Gammaglutamy l transferase ≥70 international units/L OR Alanine aminotransferase ≥70 international units/L or greater) AND Low platelets, defined as platelet count< 1003109/L AND Hemolysis, defined by abnormal (fragmented or contracted red cells) peripheral blood smear or serum lactate dehydrogenase levels≥600 international units/L or total bilirubin ≥20.5 micromole/L OR BP≥140/90 mm Hg OR Proteinuria (≥1+ 0.3 g/L on dipstick testing, a protein:creatinine ratio ≥30 mg/mmol on a random sample, or a urine protein excretion ≥300 mg /24 h")	7
Malmstrom, 2018[47]	Norway	Cohort (population-based)	418,897 pregnancies	1999 to 2014	Clinical definitions based on Norwegian Society of Obstetricians and Gynaecologists	HELLP syndrome diagnosed based on Norwegian Society of Obstetricians and Gynaecologists	8

Table S3: Characteristics of studies for cesarean section (CS) outcome

Author, year published	*Country*	*Design*	*Sample size*	*Study duration*	*Definition of chronic hypertension*	*Definition of outcome*	*Newcastle -Ottawa grade*
Sass, 1990[70]	Brazil	Case control (hospital-based)	337 births	1985 to 1986	DBP ≥90mmHg before pregnancy or up to 20 weeks of pregnancy or hypertension at 10 weeks postpartum (for those whose antenatal care was not at that hospital)	CS (not specified)	4
Hjertberg, 1992[92]	Sweden	Cohort (hospital-based)	2593 births	1986 to 1987	Chronic hypertension before pregnancy before 24weeks' gestation	CS (not specified)	6
Rey, 1994[26]	Canada	Cohort (hospital-based)	20,375 mothers	1987 to 1991	BP >140/90 mm Hg with a diagnosed before pregnancy or hypertension in at least two measurements<20 weeks of pregnancy and/or 6 weeks after delivery	CS (not specified)	6
Jain, 1997[50]	USA	Cohort (hospital-based)	109,428 mother-infant pairs	1982 to 1987	SBP≥ 140 mmHg or a DBP≥90 mmHg before pregnancy or before 20 weeks' gestation.	CS (not specified)	7
Lydakis, 1998[85]	UK	Cohort (hospital-based)	3,729 births	1980 to 1997	Hypertension (DBP ≥110 mmHg OR DBP >90 mmHg on two or more occasions ≥4 h apart) at the first booking visit before the 20 weeks' gestation in the absence of trophoblastic disease, OR hypertension at any stage of pregnancy that continued for more than 6 weeks after delivery	Emergency CS	6

Hartikainen, 1998[51]	Finland	Cohort (hospital-based)	8,050 mother-infant pairs	1985 to 1986	Hypertension diagnosed before pregnancy and/or DBP > 90 mm Hg and/or antihypertensive medication, each<20 weeks' gestation	CS (not specified)	6
Lydakis, 2001[54]	UK	Cohort (hospital-based)	238 births	1980 to 1997	Hypertension (DBP ≥110 mmHg OR DBP >90 mmHg on two or more occasions ≥4 h apart) at the first booking visit before the 20 weeks' gestation in the absence of trophoblastic disease, OR hypertension at any stage of pregnancy that continued for more than 6 weeks after delivery	Elective CS	6
Vanek, 2004[73]	Israel	Cohort (hospital-based)	114,963 mother-infant pairs	1988 to 1999	BP≥140/90 mmHg that measured at least twice at least 4 h apart that preceded pregnancy, or hypertension present before 20 weeks' gestation or that persists longer than the usual postpartum period (12 weeks post-delivery)	CS (not specified)	6
Roberts, 2005[55]	Australia	Cohort (population-based)	227,067 women and 231,811 infants	2000 to 2002	Chronic hypertension diagnosed ICD-10 codes	Emergency and elective CS	7
Gilbert, 2007[32]	USA	Cohort (population-based)	4,324,902 pregnancies	1991 to 2001	Chronic hypertension diagnosed using ICD-9 codes	CS (not specified)	8
Cruz, 2011[78]	USA	Cohort (multicentre hospital-based)	17,752 births	2002 and 2008	Hypertension reported before pregnancy, or SBP≥140 mm Hg or DBP ≥90 mm Hg before 20 weeks' gestation	CS (not specified)	7

Tuuli, 2011[59]	USA	Cohort (hospital-based)	58,135 mother-infant pairs	1990 to 2008	SBP≥ 140 mmHg or a DBP≥90 mmHg before pregnancy or before 20 weeks' gestation	CS (not specified)	8
Madi, 2012[80]	Brazil	Cohort (hospital-based)	3,689 mother-infant pairs	1998 to 2009.	BP≥140/90 mmHg that measured at least twice, before 20 weeks' gestation, or persisting for ≥12 weeks post-delivery	CS (not specified)	7
Bateman, 2012[3]	USA	Cohort (population-based)	12,947,000 pregnancies	2007 to 2008	Chronic hypertension was defined as hypertension without comorbidities using ICD-9 codes	CS (not specified)	8
Ye, 2014[62]	China	Cohort (population-based)	108,550 Pregnancies from 106, 869 women	2011 to 2011	BP≥140/90 mmHg before pregnancy or diagnosed before 20 weeks' gestation or developed hypertension after 20 weeks of gestation and continued for 12 weeks of postpartum	CS (not specified)	7
Janoudi, 2015[96]	Canada	Cohort (hospital-based)	134,088 births	2011to 2012	NR	CS (not specified)	8
Broekhuijsen, 2015[42]	Netherlands	Cohort (population-based)	988,389 mother-infant pairs	2002 to 2007	BP ≥140/90 mmHg diagnosed before pregnancy, or before 20 weeks' gestation	Elective CS	8
Panaitescu, 2017[44]	UK	Cohort (hospital-based)	109,932 pregnancies	March 2006 and July 2015/ February 2007 and November 2015	History of chronic hypertension	Emergency and elective CS	8

Table S4: Characteristics of studies for post-partum hemorrhage (PPH) outcome

Author, year published	*Country*	*Design*	*Sample size*	*Study duration*	*Definition of chronic hypertension*	*Definition of outcome*	*Newcastle-Ottawa grade*
Vanek, 2004[73]	Israel	Cohort (hospital-based)	114,963 mother-infant pairs	1988 to 1999	BP≥140/90 mmHg that measured at least twice, before 20 weeks' gestation, or persisting for ≥12 weeks post-delivery	Postpartum haemorrhage	6
Roberts, 2005[55]	Australia	Cohort (population-based)	227,067 women and 231,811 infants	2000 to 2002	ICD-10 codes	Postpartum haemorrhage	7
Gilbert, 2007[32]	USA	Cohort (population-based)	4,324,902 pregnancies	1991 to 2001	Chronic hypertension diagnosed using ICD-9 codes	Diagnosed using ICD-9 codes	8
Cruz, 2011[78]	USA	Cohort (multicentre hospital-based)	17,752	2002 and 2008	Hypertension reported before pregnancy, or SBP≥140 mm Hg or DBP ≥90 mm Hg before 20 weeks' gestation	Postpartum haemorrhage	7
Ye, 2014[62]	China	Cohort (population-based)	108,550 Pregnancies from 106, 869 women	2011 to 2011	BP≥140/90 mmHg before pregnancy or diagnosed before 20 weeks' gestation or developed hypertension after 20 weeks of gestation and continued for 12 weeks of postpartum	Postpartum haemorrhage	7
Broekhuijsen, 2015[42]	Netherlands	Cohort (population-based)	988,389 mother-infant pairs	2002 to 2007	BP ≥140/90 mmHg diagnosed before pregnancy, or before 20 weeks' gestation	Postpartum haemorrhage	8

Table S5: Characteristics of studies for maternal mortality outcome

Author, year published	*Country*	*Design*	*Sample size*	*Study duration*	*Definition of chronic hypertension*	*Definition of outcome*	*Newcastle -Ottawa grade*
Gilbert, 2007[32]	USA	Cohort (population-based)	4,324,902 pregnancies	1991 to 2001	Chronic hypertension diagnosed using ICD-9 codes	Maternal in hospital death	8
Kuklina, 2009[97]	USA	Cohort (population-based)	34,321,769 births	1998 to 2006	Chronic hypertension diagnosed using ICD-9 codes	Maternal death	8
Bateman, 2012[3]	USA	Cohort (population-based)	12,947,000 pregnancies	2007 to 2008	Chronic hypertension diagnosed using ICD-9 codes	Maternal death	8
Campbell, 2013[98]	USA	Cohort (population-based)	1,078,553	1995 to 2003	Chronic hypertension diagnosed using ICD-9 codes	Maternal death considered present if it was identified in the discharge diagnosis codes, if it was noted on the birth certificate, or if it was present on both when possible	8

Table S6: Characteristics of studies for stillbirth outcome

Author, year published	*Country (ies)*	*Design*	*Sample size*	*Study duration*	*Definition of chronic hypertension*	*Definition of outcome*	*Newcastle -Ottawa grade*
Copper, 1994[99]	USA	Cohort (population-based)	34,350 births	1982-1986	NR	Birth of a fetus at 20 weeks' gestation or later with an APGAR score of 0 at 1 and 5 minutes	7
Ananth, 1995a[93]	USA	Cohort (population-based)	371,123 mother-infant pairs	1988 and 1991	NR	Fetal death (early≤20 weeks and late>28 weeks) and further defined into antepartum and intrapartum death	8
Jain, 1997[50]	USA	Cohort (hospital-based)	109,428 mother-infant pairs	1982 to 1987	SBP≥ 140 mmHg or a DBP≥90 mmHg before pregnancy or before 20 weeks' gestation	***NR***	7
Lydakis, 1998[85]	UK	Cohort (hospital-based)	3,729 births	1980 to 1997	Hypertension (DBP ≥110 mmHg OR DBP >90 mmHg on two or more occasions ≥4 h apart) at the first booking visit before the 20 weeks' gestation in the absence of trophoblastic disease, OR hypertension at any stage of pregnancy that continued for more than 6 weeks after delivery	Intrauterine fetal death at >24 weeks' gestation with an Apgar score 0 at 1 min	6
Conde-Agudelo, 2000b[100]	Latin America and the Caribbean*	Cohort (multicountry)	837,232 births	1985 to 1997	History of chronic hypertension using ICD-10 codes	Fetal death at≥20 weeks' gestation	7
Allen, 2004[72]	Canada	Cohort (population-based)	123,160 births	1988 to 2000	Hypertension reported before pregnancy, or prior to 20 weeks' gestation	Fetal death at≥20 weeks' gestation and birthweight ≥ 500 grams	9

Canterino, 2004[94]	USA	Cohort (population-based)	21,610,873 mother-infant pairs	1995 to 2000	Hypertension before pregnancy or before 20 weeks' gestation	Fetal death at≥24 weeks' gestation	7
Roberts, 2005[55]	Australia	Cohort (population-based)	227,067 women and 231,811 infants	2000 to 2002	Chronic hypertension diagnosed using ICD-10 codes	Fetal death at≥20 weeks' gestation	7
Aagaard-Tillery, 2006[101]	USA	Case control (population-based)	4306	1992 to 2002	NR	Fetal death at≥20 weeks' gestation or weighing ≥400g	6
Gilbert, 2007[32]	USA	Cohort (population-based)	4,324,902 pregnancies	1991 to 2001	Chronic hypertension diagnosed using ICD-9 codes	ICD-9 –CM codes	8
Zetterstrom, 2008[90]	Sweden	Cohort (population-based)	866,188 mother-infant pairs	1992 to 2004	BP≥140/90 mmHg diagnosed before pregnancy, or before 20 weeks' gestation using (ICD-9 and ICD-10 codes)	Intrauterine fetal death at ≥28 weeks' gestation	8
Reddy, 2010[102]	USA	Cohort (population-based)	160,954	2002 to 2008	Chronic hypertension diagnosed using ICD-9 codes	Antepartum stillbirth defined as fetus having no signs of life before labor with an Apgar scores of 0 and 0 at 1 minute and 5 minutes	7
Tuuli, 2011[59]	USA	Cohort (hospital-based)	58,135 mother-infant pairs	1990 to 2008	SBP≥ 140 mmHg or a DBP≥90 mmHg before pregnancy or before 20 weeks' gestation	Fetal death at≥20 weeks' gestation	8
Yanit, 2012[34]	USA	Cohort (population-based)	527,937 mother-infant pairs	2006	Chronic hypertension diagnosed using ICD-9 codes	NR	8
Bateman, 2012[3]	USA	Cohort (population-based)	12,947,000 pregnancies	2007 to 2008	Chronic hypertension diagnosed using ICD-9 codes	ICD-9 codes	8

Ahmad, 2012[91]	Norway	Cohort (population-based)	2,027,042 mother-infant pairs	1967 to 2006	SBP≥ 140 mmHg or a DBP≥90 mmHg before 20 weeks' gestation (ICD-8 and ICD-10 codes)	Fetal death ≥20 weeks' gestation	7
Madi, 2012[80]	Brazil	Cohort (hospital-based)	3,689 mother-infant pairs	1998 to 2009.	BP≥140/90 mmHg that measured at least twice, before 20 weeks' gestation, or persisting for ≥12 weeks post-delivery	Fetal death	7
Yerlikaya, 2016[103]	UK	Cohort (hospital-based)	113,415 mother-infant pairs	2006 to 2015	History of chronic hypertension	Fetal death ≥24 weeks' gestation	8
Panaitescu, 2017[44]	UK	Cohort (hospital-based)	109,932 pregnancies	March 2006 and July 2015/ February 2007 and November 2015	History of chronic hypertension	Fatal death ≥24 weeks	8
Xiong, 2018[104]	China	Cohort (population-based)	6,970,032 births	2012 to 2016	SBP≥ 140 mmHg or a DBP≥90 mmHg before pregnancy or before 20 weeks' gestation.	Stillbirth defined according to WHO of 3rd trimester stillbirth definition	8
Youngstrom, 2018[45]‡	USA	Cohort (hospital-based)	1,306 mother-infant pairs	2000 to 2014	History of hypertension **or** the use of antihypertensive medication before pregnancy	NR	8

*Uruguay, Argentina, Peru, Colombia, Honduras, Paraguay, Salvador, Chile , Bolivia, Costa Rica, Panama, Dominican Republic, Nicaragua, Brazil, Ecuador, Mexico, Bahamas, and Venezuela. ‡ Odds ratios from this study was combined for treated and untreated women with chronic hypertension.

Table S7: Characteristics of studies for very preterm birth (VPTB) outcome

Author, year published	*Country*	*Design*	*Sample size*	*Study duration*	*Definition of chronic hypertension*	*Definition of outcome*	*Newcastle -Ottawa grade*
Ananth, 1995b[9]	USA	Cohort (population-based)	276,876	1988 and 1990	Chronic hypertension obtained from medical records; no further details provided	<33 weeks' gestation	8
McCowan, 1996[49]	New Zealand	Cohort (hospital-based)	20,224 mother-infant pairs	1991 to 1993	DBP>90 mmHg before 20 weeks gestation, pre-existing history of essential hypertension and/or on antihypertensive medication before the pregnancy	<32 weeks' gestation	6
Roberts, 2005[55]	Australia	Cohort (population-based)	227,067 women and 231,811 infants	2000 to 2002	chronic hypertension diagnosed using ICD-10 codes	28-32 weeks' gestation	*7*
Tuuli, 2011[59]	USA	Cohort (hospital-based)	58,135 mother-infant pairs	1990 to 2008	SBP≥ 140 mmHg or a DBP≥90 mmHg before pregnancy or before 20 weeks' gestation	<32 weeks' gestation	*8*
Ferrazzani, 2011[58]	Italy	Cohort (hospital-based)	1,154 Women	1986 and 1995	Hypertension diagnosed before pregnancy and/or DBP ≥90 mm Hg and/or on antihypertensive medication, each before 20 weeks' gestation uncomplicated by de novo proteinuria	<32 weeks' gestation	6
Yanit, 2012[34]	USA	Cohort (population-based)	527,937 mother-infant pairs	2006	Chronic hypertension diagnosed using ICD-9 codes	<32 weeks' gestation	8
Broekhuijsen, 2015[42]	Netherlands	Cohort (population-based)	988,389 mother-infant pairs	2002 to 2007	BP ≥140/90 mmHg diagnosed before pregnancy, or before 20 weeks' gestation	<32 weeks' gestation	8
Yang, 2015[66]	China	Cohort (national-based)	344,929	2010 and 2013	SBP≥ 140 mmHg or a DBP≥90 mmHg on a single occasion after participants rested for ≥10 minutes	<32 weeks' gestation, but after 28 weeks	6

Panaitescu, 2017[44]	UK	Cohort (hospital-based)	109,932 pregnancies	March 2006 and July 2015/ February 2007 and November 2015	History of chronic hypertension	<34 weeks' gestation (medically indicated and spontaneous) *	8

**we combined the estimates for both medically indicated and spontaneous as it was the only study reported that for VPTB*

Table S8: Characteristics of studies for preterm birth (PTB) outcome

Author, year published	*Country (ies)*	*Design*	*Sample size*	*Study duration*	*Definition of chronic hypertension*	*Definition of outcome*	*Newcastle -Ottawa grade*
Acien,1990[48]	Spain	Cohort (hospital-based)	236 pregnancies and 238 newborns	1979 and 1986	NR	33-36 weeks' gestation	4
Rey, 1994[26]	Canada	Cohort (hospital-based)	20,375 mothers	1987 to 1991	BP>140/90 mm Hg with a diagnosed before pregnancy or hypertension in at least two measurements<20 weeks of pregnancy and/or 6 weeks after delivery	NR	6
Velentgas, 1994[84]	USA	Cohort (population-based)	14,562 mother-infant pairs	1984-1990	NR	<37 weeks' gestation	6
Ananth, 1995b[9]	USA	Cohort (population-based)	276,876	1988 and 1990	Chronic hypertension obtained from medical records; no further details provided	<37 weeks' gestation	8
McCowan, 1996[49]	New Zealand	Cohort (hospital-based)	20,224 mother-infant pairs	1991 to 1993	DBP>90 mmHg before 20 weeks gestation, pre-existing history of essential hypertension and/or on antihypertensive medication before the pregnancy	<37 weeks' gestation	6
Jain, 1997[50]	USA	Cohort (hospital-based)	109,428 mother-infant pairs	1982 to 1987	SBP≥ 140 mmHg or a DBP≥90 mmHg before pregnancy or before 20 weeks' gestation.	NR	7
Hartikainen, 1998[51]	Finland	Cohort (hospital-based)	8,050 mother-infant pairs	1985 to 1986	Hypertension diagnosed before pregnancy and/or DBP >90 mm Hg and/ or antihypertensive medication, each<20 weeks' gestation	<37 weeks' gestation	6
Meis, 1998[52]	USA	Cohort (multi-centres)	2929 Women	1992 to 1994	BP≥140/90 mmHg before 20 weeks' gestation	<37 weeks' gestation (<259 days') gestation, (medically indicated)	7

Samadi, 1998[53]	USA	Case control (hospital-based)	25,060	1988 and 1993	Chronic hypertension diagnosed using ICD-9 codes	<37 weeks' gestation (spontaneous)	7
Lydakis, 2001[54]	UK	Cohort (hospital-based)	238 births	1980 to 1997	Hypertension (DBP ≥110 mmHg OR DBP >90 mmHg on two or more occasions ≥4 h apart) at the first booking visit before the 20 weeks' gestation in the absence of trophoblastic disease, OR hypertension at any stage of pregnancy that continued for more than 6 weeks after delivery	<37 weeks' gestation	6
Roberts, 2005[55]	Australia	Cohort (population-based)	227,067 women and 231,811 infants	2000 to 2002	Chronic hypertension diagnosed using ICD-10 codes	33-36 weeks' gestation	7
Graham, 2007[56]	USA	Cohort (population-based)	202,931 mother-infant pairs	1999 to 2003	Hypertension diagnosed before pregnancy	<37 weeks' gestation	7
Gilbert, 2007[32]	USA	Cohort (population-based)	4,324,902 pregnancies	1991 to 2001	Chronic hypertension diagnosed using ICD-9 codes	<37 weeks' gestation	8
Carter, 2011[57]	USA	Cohort (population-based)	259,576 Births	2000 to 2008	NR	<37 weeks' gestation	6
Ferrazzani, 2011[58]	Italy	Cohort (hospital-based)	1,154 Women	1986 and 1995	Hypertension diagnosed before pregnancy and/or DBP ≥90 mm Hg and/or on antihypertensive medication, each before 20 weeks' gestation uncomplicated by de novo proteinuria	<37 weeks' gestation	6
Tuuli, 2011[59]	USA	Cohort (hospital-based)	58,135 mother-infant pairs	1990 to 2008	SBP≥ 140 mmHg or a DBP≥90 mmHg before pregnancy or before 20 weeks' gestation	<37 weeks' gestation	8

Bateman, 2012[3]	USA	Cohort (population-based)	12,947,000 pregnancies	2007 to 2008	Chronic hypertension diagnosed using ICD-9 codes	<37 weeks' gestation (spontaneous)	8
Yanit, 2012[34]	USA	Cohort (population-based)	527,937 mother-infant pairs	2006	Chronic hypertension diagnosed using ICD-9 codes	<37 weeks' gestation	8
Orbach, 2013[35‡]	Israel	Cohort (population-based)	100,029 births	1998 to 2008	Chronic hypertension diagnosed using ICD-9 codes	<37 weeks' gestation	8
Su, 2013[60]	Taiwan	Cohort (population-based)	10,908 mother-infant pairs	2005 to 2005	Chronic hypertension diagnosed using ICD-9-CM codes	<37 weeks' gestation	8
Morisaki, 2014[61]	29 countries*	Cohort (international, multicountry)	299,878 women	2010 to 2011	NR	<37 weeks' gestation	7
Ye, 2014[62]	China	Cohort (population-based)	108,550 Pregnancies from 106, 869 women	2011 to 2011	BP≥140/90 mmHg before pregnancy or diagnosed before 20 weeks' gestation or developed hypertension after 20 weeks of gestation and continued for 12 weeks of postpartum	<37 weeks' gestation (after 20 weeks and before 37)	7
Arora, 2015[63]	5 countries**	Cohort (multicountry)	37 661 births	2007 to 2009	History of chronic hypertension	<37 weeks' gestation	6
Broekhuijsen, 2015[42]	Netherlands	Cohort (population-based)	988,389 mother-infant pairs	2002 to 2007	BP ≥140/90 mmHg diagnosed before pregnancy, or before 20 weeks' gestation	<37 weeks' gestation	8
Derakhshi, 2014[64]	Iran	Case control (hospital-based)	600 births	2012	NR	<37 weeks' gestation	5

Tucker, 2015[65]	USA	Cohort (Medicaid patients)	15,428 women	2011 to 2012	NR	24–36 weeks' gestation	7
Yang, 2015[66]	China	Cohort (national-based)	344,929	2010 and 2013	SBP≥ 140 mmHg or a DBP≥90 mmHg on a single occasion after participants rested for ≥10 minutes	<37 weeks' gestation	6
Premkumar, 2016[67]	USA	Cohort (hospital-based)	23,425 women	2002 to 2015	SBP> 140 mm Hg or DBP> 90 mm Hg recorded on at least 2 separate occasions >6 hours apart before 20 weeks' gestation	<37 weeks' gestation< 37 weeks' gestation (medically indicated and spontaneous)	9
Souza, 2016[68]	Brazil	Case control (multicentre)	2614 Births	2011 to 2012	NR	<37 weeks' gestation	6
Panaitescu, 2017[44]	UK	Cohort (hospital-based)	109,932 pregnancies	March 2006 and July 2015/ February 2007 and Novembe r 2015	History of chronic hypertension	<37 weeks' gestation (medically indicated and spontaneous)	8
Campbell, 2018[69]	Canada	Cohort (population-based)	26,654 live births	2009 to 2014	NR	<37 weeks' gestation (live births)	6
Youngstrom, 2018[45‡]	USA	Cohort (hospital-based)	1,306 mother-infant pairs	2000 to 2014	History of hypertension or the use of antihypertensive medication before pregnancy	<37 weeks' gestation	8

*29 countries: African Region (Angola, DR Congo, Kenya, Niger, Nigeria and Uganda); Region of the Americas (Argentina, Brazil, Ecuador, Mexico, Nicaragua, Paraguay and Peru); Eastern Mediterranean Region (Afghanistan, Jordan, Lebanon, occupied Palestinian territory, Palestine, Pakistan and Qatar); South-East Asia Region (India, Nepal, Sri Lanka and Thailand); Western Pacific Region (Cambodia, China, Japan, Mongolia, Philippines and Vietnam)

** Czech Republic, Hungary, Romania, Slovakia, and Ukraine

‡ The ORs from these studies were combined for treated and untreated women with chronic hypertension.

Table S9: Characteristics of studies for small for gestational age (SGA) outcome

Author, year published	*Country (ies)*	*Design*	*Sample size*	*Study duration*	*Definition of chronic hypertension*	*Definition of outcome*	*Newcastle -Ottawa grade*
Sass, 1990[70]	Brazil	Case control (hospital-based)	337 Births	1985 to 1986	DBP ≥90mmHg before pregnancy or up to 20 weeks' gestation or hypertension at 10 weeks postpartum (for those whose antenatal care was not at that hospital).	birthweight <10th percentile for gestational age	4
Acien,1990[48]	Spain	Cohort (hospital-based)	236 pregnancies and 238 newborns	1979 and 1986	NR	birthweight <10th percentile for gestational age	4
Rey, 1994[26]	Canada	Cohort (hospital-based)	20,375 mothers	1987 to 1991	BP>140/90 mm Hg with a diagnosed before pregnancy or hypertension in at least two measurements<20 weeks of pregnancy and/or 6 weeks after delivery	birthweight <10th percentile for gestational age	6
Ananth, 1995b[9]	USA	Cohort (population-based)	276,876	1988 and 1990	Chronic hypertension obtained from medical records; no further details provided	birthweight <10th percentile for gestational age	8
McCowan, 1996[49]	New Zealand	Cohort (hospital-based)	20,224 mother-infant pairs	1991 to 1993	DBP>90 mmHg before 20 weeks gestation, pre-existing history of essential hypertension and/or on antihypertensive medication before the pregnancy	birthweight <5th percentile for gestational age	6
Haelterman, 1997[71]	France	Cohort (multicentre)	1938 mother-infant pairs	1991 to 1993	DBP ≥90 mmHg on two or more consecutive occasions at least 4 h apart or SBP>160 mmHg before 21 weeks' gestation OR women with a prior history of hypertension and were on antihypertensive treatment.	birthweight <5th percentile for gestational age	6

Jain, 1997[50]	USA	Cohort (hospital-based)	109,428 mother-infant pairs	1982 to 1987	SBP≥ 140 mmHg or a DBP≥90 mmHg before pregnancy or before 20 weeks' gestation.	Intrauterine growth restriction (NR)	7
Hartikainen, 1998[51]	Finland	Cohort (hospital-based)	8,050 mother-infant pairs	1985 to 1986	Hypertension diagnosed before pregnancy and/or DBP > 90 mm Hg and/ or antihypertensive medication, each<20th week	birthweight <10th percentile for gestational age	6
Lydakis, 2001[54]	UK	Cohort (hospital-based)	238 births	1980 to 1997	Hypertension (DBP ≥110 mmHg OR DBP >90 mmHg on two or more occasions ≥4 h apart) at the first booking visit before the 20th week of pregnancy in the absence of trophoblastic disease, OR hypertension at any stage of pregnancy that continued for more than 6 weeks after delivery.	birthweight <5th percentile for gestational age	6
Allen, 2004[72]	Canada	Cohort (population-based)	123,160 births	1988 to 2000	Hypertension reported before pregnancy, or before to 20 weeks' gestation	birthweight <5th percentile for gestational age	9
Vanek, 2004[73]	Israel	Cohort (hospital-based)	114,963 mother-infant pairs	1988 to 1999	BP≥140/90 mmHg that measured at least twice, before 20 weeks' gestation, or persisting for ≥12 weeks post-delivery	NR	6
Roberts, 2005[55]	Australia	Cohort (population-based)	227,067 women and 231,811 infants	2000 to 2002	chronic hypertension diagnosed using ICD-10 codes	birthweight <10th percentile for gestational age	7
Odibo, 2006[74]	USA	Case control (hospital-based)	2472	1997 to 2004	NR	birthweight <10th percentile for gestational age	7

Rasmussen, 2006[75]	Norway	Cohort (population-based)	404,400 mother-infant pairs	1999 to 2002	NR	birthweight <10th percentile for gestational age	6
Zetterstrom, 2006[76]	Sweden	Cohort (population-based)	560,188 mother-infant pairs	1992 to 1998	BP≥140/90 mmHg diagnosed before pregnancy, or before 20 weeks' gestation using (ICD-9 and ICD-10 codes)	<2 standard deviations below the mean birth weight adjusted for gestational age and sex	8
Gilbert, 2007[32]	USA	Cohort (population-based)	4,324,902 pregnancies	1991 to 2001	Chronic hypertension diagnosed using ICD-9 codes	ICD-9 codes	8
Catov, 2008[77]	Denmark	Cohort (national-based)	81,008 mother-infant pairs	1996 to 2002	Hypertension reported before pregnancy or at the first interview (16 weeks), and/or reported taking antihypertensive medication	<2 standard deviations below the mean birth weight	8
Cruz, 2011[78]	USA	Cohort (multicentre hospital-based)	17,752	2002 and 2008	Hypertension reported before pregnancy, or SBP≥140 mm Hg or DBP ≥90 mm Hg before 20 weeks' gestation	birthweight <10th percentile for gestational age	7
Poon, 2011[79]	UK	Cohort (hospital-based)	33,602 pregnancies	2006 to 2009	History of chronic hypertension	birthweight <5th percentile for gestational age	6
Tuuli, 2011[59]	USA	Cohort (hospital-based)	58,135 mother-infant pairs	1990 to 2008	SBP≥ 140 mmHg or a DBP≥90 mmHg before pregnancy or before 20 weeks' gestation	birthweight <10th percentile for gestational age	8
Bateman, 2012[3]	USA	Cohort (population-based)	12,947,000 pregnancies	2007 to 2008	Chronic hypertension diagnosed using ICD-9 codes	ICD-9 codes	8
Madi, 2012[80]	Brazil	Cohort (hospital-based)	3,689 mother-infant pairs	1998 to 2009.	BP≥140/90 mmHg that measured at least twice, before 20 weeks' gestation, or persisting for ≥12 weeks post-delivery	NR	7

Yanit, 2012[35]	USA	Cohort (population-based)	527,937 mother-infant pairs	2006	Chronic hypertension diagnosed using ICD-9 codes	birthweight <10th percentile for gestational age	8
Anderson, 2013[81]	New Zealand	Cohort (population-based)	24,434 mother-infant pairs	2006 to 2009	Chronic hypertension diagnosed based on the International Society for the Study of Hypertension in Pregnancy guidelines	birthweight <10th percentile for gestational age	8
Orbach, 2013[35‡]	Israel	Cohort (population-based)	100,029 births	1998 to 2008	Chronic hypertension diagnosed using ICD-9 codes	ICD-9 codes	8
Su, 2013[60]	Taiwan	Cohort (population-based)	10,908 mother-infant pairs	2005 to 2005	Chronic hypertension diagnosed using ICD-9 CM codes	birthweight <10th percentile for gestational age	8
Ota, 2014[82]	29 countries*	Cohort (international, multicountry)	245,773 mother-infant pairs	2010 to 2011	NR	birthweight <10th percentile for gestational age	7
Xaverius, 2014[83]	USA	Cohort (population-based)	142,017 mother-infant pairs	2000-2009	History of chronic hypertension	birthweight <10th percentile for gestational age	7
Broekhuijsen, 2015[42]	Netherlands	Cohort (population-based)	988,389 mother-infant pairs	2002 to 2007	BP ≥140/90 mmHg diagnosed before pregnancy, or before 20 weeks' gestation	birthweight <10th percentile for gestational age	8
Panaitescu, 2017[44]	UK	Cohort (hospital-based)	109,932 pregnancies	March 2006 and July 2015/ February 2007 and November 2015	History of chronic hypertension	birthweight <10th percentile for gestational age	8

Campbell, 2018[69]	Canada	Cohort (population-based)	26,654 live births	2009 to 2014	NR	birthweight <10th percentile for gestational age	6
Youngstrom, 2018[45]‡	USA	Cohort (hospital-based)	1,306 mother-infant pairs	2000 to 2014	History of hypertension or the use of antihypertensive medication before pregnancy	birthweight <10th percentile for gestational age	8

*29 countries: African Region (Angola, DR Congo, Kenya, Niger, Nigeria and Uganda); Region of the Americas (Argentina, Brazil, Ecuador, Mexico, Nicaragua, Paraguay and Peru); Eastern Mediterranean Region (Afghanistan, Jordan, Lebanon, occupied Palestinian territory, Palestine, Pakistan and Qatar); South-East Asia Region (India, Nepal, Sri Lanka and Thailand); Western Pacific Region (Cambodia, China, Japan, Mongolia, Philippines and Vietnam)

‡ The ORs from these studies were combined for treated and untreated women with chronic hypertension.

Table S10: Characteristics of studies for low birth weight (LBW) outcome

Author, year published	*Country*	*Design*	*Sample size*	*Study duration*	*Definition of chronic hypertension*	*Definition of outcome*	*Newcastle -Ottawa grade*
Velentgas, 1994[84]	USA	Cohort (population-based)	14,562 mother-infant pairs	1984-1990	NR	birth weight of <2500 grams	6
Ananth, 1995b[9]	USA	Cohort (population-based)	276,876	1988 and 1990	Chronic hypertension obtained from medical records; no further details provided	birth weight of <2500 grams‡	8
Hartikainen, 1998[51]	Finland	Cohort (hospital-based)	8,050 mother-infant pairs	1985 to 1986	Hypertension diagnosed before pregnancy and/or DBP > 90 mm Hg and/or antihypertensive medication, each<20 weeks' gestation	birth weight of <2500 grams	6
Lydakis, 1998[85]	UK	Cohort (hospital-based)	3,729 births	1980 to 1997	Hypertension (DBP ≥110 mmHg OR DBP >90 mmHg on two or more occasions ≥4 h apart) at the first booking visit before the 20 weeks' gestation in the absence of trophoblastic disease, OR hypertension at any stage of pregnancy that continued for more than 6 weeks after delivery	birth weight of <2000 grams	6
Gilbert, 2007[32]	USA	Cohort (population-based)	4,324,902 pregnancies	1991 to 2001	Chronic hypertension diagnosed using ICD-9 codes	birth weight of ≤2500 grams	8
Graham, 2007[56]	USA	Population-based	202,931 mother-infant pairs	1999 to 2003	Hypertension diagnosed before pregnancy	birth weight of <2500 grams	7
Odell, 2006[86]	USA	Population-based (Black women only)	16,578	1996 to 2000	History of chronic hypertension diagnosed using ICD 9 codes	birth weight of <2500 grams	7

Vahdaninia, 2008[87]	Iran	Cohort (hospital-based)	3733 mother-infant pairs	2005	NR	birth weight of <2500 grams	7
Madi, 2012[80]	Brazil	Cohort (hospital-based)	3,689 mother-infant pairs	1998 to 2009.	BP≥140/90 mmHg that measured at least twice, before 20 weeks' gestation, or persisting for ≥12 weeks post-delivery	birth weight of ≤2500 grams	7
Su, 2013[60]	Taiwan	Cohort (population-based)	10,908 mother-infant pairs	2005 to 2005	Chronic hypertension diagnosed using ICD-9 CM codes	birth weight of <2500 grams	8
Ye, 2014[62]	China	Cohort (population-based)	108,550 Pregnancies from 106, 869 women	2011 to 2011	BP≥140/90 mmHg before pregnancy or diagnosed before 20 weeks' gestation or developed hypertension after 20 weeks of gestation and continued for 12 weeks of postpartum	birth weight of <2500 grams	7
Harvey, 2017[88]	USA	Case control (hospital-based)	862 births	2010 to 2011	NR	birth weight of <2500 grams	8
Campbell, 2018[69]	Canada	Cohort (population-based)	26,654 live births	2009 to 2014	NR	birth weight of <2500 grams	6
Hailu,2018[89]	Ethiopia	Case control (hospital-based)	441 births	2016	NR	birth weight of <2500 grams	6

‡ We combined the ORs for birthweight < 1,499 g and birthweight (1,500-2,499 g).

Table S11: Characteristics of studies for neonatal death outcome

Author, year published	*Country*	*Design*	*Sample size*	*Study duration*	*Definition of chronic hypertension*	*Definition of outcome*	*Newcastle -Ottawa grade*
Jain, 1997[50]	USA	Cohort (hospital-based)	109,428 mother-infant pairs	1982 to 1987	SBP≥ 140 mmHg or a DBP≥90 mmHg before pregnancy or before 20 weeks' gestation.	NR	7
Gilbert, 2007[32]	USA	Cohort (population-based)	4,324,902 pregnancies	1991 to 2001	Chronic hypertension diagnosed using ICD-9 codes	ICD-9 –CM codes	8
Zetterstrom, 2008[90]	Sweden	Cohort (population-based)	866,188 mother-infant pairs	1992 to 2004	BP≥140/90 mmHg diagnosed before pregnancy, or before 20 weeks' gestation using (ICD-9 and ICD-10 codes)	Neonatal death of an infant born live at any week of gestation, within 27 days of birth	8
Madi, 2012[80]	Brazil	Cohort (hospital-based)	3,689 mother-infant pairs	1998 to 2009.	BP≥140/90 mmHg that measured at least twice, before 20 weeks' gestation, or persisting for ≥12 weeks post-delivery	Neonatal mortality	7
Youngstrom, 2018[45‡]	USA	Cohort (hospital-based)	1,306 mother-infant pairs	2000 to 2014	History of hypertension or the use of antihypertensive medication before pregnancy	NR	8

‡ The ORs from this study was combined for treated and untreated women with chronic hypertension.

Table S12: Characteristics of studies for perinatal death outcome

Author, year published	*Country*	*Design*	*Sample size*	*Study duration*	*Definition of chronic hypertension*	*Definition of outcome*	*Newcastle -Ottawa grade*
Acien,1990[48]	Spain	Cohort (hospital-based)	236 pregnancies and 238 newborns	1979 and 1986	NR	Late fetal death with a birth weight≥1000 g, and early neonatal death<less 7 days	4
Sass, 1990[70]	Brazil	Case control (hospital-based)	337 Births	1985 to 1986	DBP ≥90mmHg before pregnancy or up to 20 weeks of pregnancy or hypertension at 10w postpartum (for those whose antenatal care was NOT at that hospital).	NR	4
Rey, 1994[26]	Canada	Cohort (hospital-based)	20,375 mothers	1987 to 1991	BP>140/90 mm Hg with a diagnosed before pregnancy or hypertension in at least two measurements<20 weeks of pregnancy and/or 6 weeks after delivery	NR	6
McCowan, 1996[49]	New Zealand	Cohort (hospital-based)	20,224 mother-infant pairs	1991 to 1993	DBP>90 mmHg before 20 weeks gestation, pre-existing history of essential hypertension and/or on antihypertensive medication before the pregnancy	Fetal deaths after 20 weeks, early and late neonatal deaths per 1000 total births	6
Jain, 1997[50]	USA	Cohort (hospital-based)	109,428 mother-infant pairs	1982 to 1987	SBP≥ 140 mmHg or a DBP≥90 mmHg before pregnancy or before 20 weeks' gestation.	NR	7

Hartikainen, 1998[51]	Finland	Cohort (hospital-based)	8,050 mother-infant pairs	1985 to 1986	Hypertension diagnosed before pregnancy and/or DBP > 90 mm Hg and/or antihypertensive medication, each<20 weeks' gestation	Fetal death with a birth weight≥ 500 g, and/or gestational age≥ 24 completed weeks, and neonatal death<less 7 days	6
Vanek, 2004[73]	Israel	Cohort (hospital-based)	114,963 mother-infant pairs	1988 to 1999	BP≥140/90 mmHg that measured at least twice, before 20 weeks' gestation, or persisting for ≥12 weeks post-delivery	NR	6
Ahmad, 2012[91]	Norway	Cohort (population-based)	2,027,042 mother-infant pairs	1967 to 2006	SBP≥ 140 mmHg or a DBP≥90 mmHg before 20 weeks' gestation using (ICD-8 and ICD-10 codes)	Fetal death with a birth weight≥ 500 g, and/or gestational age≥22 weeks (154 days) and neonatal death<less 7 days	7
Ye, 2014[62]	China	Cohort (population-based	108,550 Pregnancies from 106, 869 women	2011 to 2011	BP≥140/90 mmHg before pregnancy or diagnosed before 20 weeks' gestation or developed hypertension after 20 weeks of gestation and continued for 12 weeks of postpartum	Fetuses and neonates who were born dead, or died in the first 28 days after delivery	7
Broekhuijsen, 2015[42]	Netherlands	Cohort (population-based)	988,389 mother-infant pairs	2002 to 2007	BP ≥140/90 mmHg diagnosed before pregnancy, or before 20 weeks' gestation	Fetal death or neonatal death within 7 days after birth	8
Youngstrom, 2018[45‡]	USA	Cohort (hospital-based)	1,306 mother-infant pairs	2000 to 2014	History of hypertension or the use of antihypertensive medication before pregnancy	NR	8

‡ The ORs from this study was combined for treated and untreated women with chronic hypertension.

Table S13: Characteristics of studies for neonatal intensive care unit (NICU) admission outcome

Author, year published	*Country*	*Design*	*Sample size*	*Study duration*	*Definition of chronic hypertension*	*Definition of outcome*	*Newcastle-Ottawa grade*
Hjertberg, 1992[92]	Sweden	Cohort (hospital-based)	2593	1986 to 1987	Chronic hypertension before pregnancy and/or before 24 weeks' gestation	Admission to NICU	***6***
McCowan, 1996[49]	New Zealand	Cohort (hospital-based)	20,224 mother-infant pairs	1991 to 1993	DBP>90 mmHg before 20 weeks gestation, pre-existing history of essential hypertension and/or on antihypertensive medication before the pregnancy	Admission to NICU	6
Hartikainen, 1998[51]	Finland	Cohort (hospital-based)	8,050 mother-infant pairs	1985 to 1986	Hypertension diagnosed before pregnancy and/or DBP > 90 mm Hg and/or antihypertensive medication, each<20 weeks' gestation	Admission to NICU	6
Roberts, 2005[55]	Australia	Cohort (population-based)	227,067 women and 231,811 infants	2000 to 2002	Chronic hypertension diagnosed using ICD-10 codes	Admission to NICU	***7***
Tuuli, 2011[59]	USA	Cohort (hospital-based)	58,135 mother-infant pairs	1990 to 2008	SBP≥ 140 mmHg or a DBP≥90 mmHg before pregnancy or before 20 weeks' gestation	Admission to NICU	***8***
Cruz, 2011[78]	USA	Cohort (Multicentre hospital- based)	17,752	2002 and 2008	Hypertension reported before pregnancy, or SBP≥140 mm Hg or DBP ≥90 mm Hg before 20 weeks' gestation	Admission to NICU	***7***
Madi, 2012[80]	Brazil	Cohort (hospital-based)	3,689 mother-infant pairs	1998 to 2009.	BP≥140/90 mmHg that measured at least twice, before 20 weeks' gestation, or persisting for ≥12 weeks post-delivery	Admission to NICU	***7***

Table S14: Characteristics of studies for miscarriage outcome

Author, year published	*Country*	*Design*	*Sample size*	*Study duration*	*Definition of chronic hypertension*	*Definition of outcome*	*Newcastle -Ottawa grade*
Sass, 1990[70]	Brazil	Case control (hospital-based)	337 Births	1985 to 1986	DBP ≥90mmHg before pregnancy or up to 20 weeks of pregnancy or hypertension at 10w postpartum (for those whose antenatal care was NOT at that hospital).	NR	4
Panaitescu, 2017[44]	UK	Cohort (hospital-based)	109,932 pregnancies	March 2006 and July 2015/ February 2007 and November 2015	History of chronic hypertension	Late miscarriage included spontaneous delivery or fetal death at 16 + 0 to 23 + 6 weeks' gestation	8

Table S15: Characteristics of studies for stillbirth stratified by maternal ethnicity

Author, year published	*Country*	*Design*	*Sample size*	*Study duration*	*Definition of chronic hypertension*	*Definition of outcome*	*Newcastle -Ottawa grade*
Ananth, 1995a[93]	USA	Cohort (population-based)	Black:14,417 White:15,819	1988 and 1990	Chronic hypertension obtained from medical records; no further details provided	Fetal death at≥20 weeks' gestation	8
Canterino, 2004[94]	USA	Cohort (population-based)	Black:3,269,211 White:18,341,662	1995 to 2000	Hypertension before pregnancy or before 20 weeks' gestation	Fetal death at≥24 weeks' gestation	7

Table S16: Characteristics of studies for PTB stratified by maternal ethnicity

Author, year published	*Country*	*Design*	*Sample size*	*Study duration*	*Definition of chronic hypertension*	*Definition of outcome*	*Newcastle -Ottawa grade*
Ananth, 1995b[9]	USA	Cohort (population-based)	Black:14,417 White:15,819	1988 and 1990	Chronic hypertension obtained from medical records; no further details provided	<37 weeks' gestation	8
Rey, 1997[95]	Canada	Cohort (hospital-based)	Black:2,450 White:17,854	1987 to 1991	BP>140/90 mm Hg with a diagnosed before pregnancy or hypertension in at least two measurements<20 weeks of pregnancy and/or 6 weeks after delivery	Prematurity/NR	6
Samadi, 1998[53]	USA	Case control (hospital-based)	Black:25,060 White: none	1988 and 1993	Chronic hypertension diagnosed using ICD-9 codes	<37 weeks' gestation	7
Graham, 2007[56]	USA	Cohort (population-based)	Black:91,718 White:111,213	1999 to 2003	Hypertension diagnosed before pregnancy	<37 weeks' gestation	7
Premkumar, 2016[67]	USA	Cohort (hospital-based)	Black:2,272 White:10,843	2002 to 2015	SBP> 140 mm Hg or DBP> 90 mm Hg recorded on at least 2 separate occasions >6 hours apart before 20 weeks' gestation	<37 weeks' gestation	9

Table S17: Characteristics of studies for SGA stratified by maternal ethnicity

Author, year published	*Country*	*Design*	*Sample size*	*Study duration*	*Definition of chronic hypertension*	*Definition of outcome*	*Newcastle -Ottawa grade*
Rey, 1997[95]	Canada	Cohort (hospital-based)	Black:2,450 White:17,854	1987 to 1991	BP>140/90 mm Hg with a diagnosed before pregnancy or hypertension in at least two measurements<20 weeks of pregnancy and/or 6 weeks after delivery	Prematurity/NR	6
Ananth, 1995b[9]	USA	Cohort (population-based)	Black:14,417 White:15,819	1988 and 1990	Chronic hypertension obtained from medical records; no further details provided	<37 weeks' gestation	8

Table S18: Characteristics of studies for LBW stratified by maternal ethnicity

Author, year published	*Country*	*Design*	*Sample size*	*Study duration*	*Definition of chronic hypertension*	*Definition of outcome*	*Newcastle -Ottawa grade*
Velentgas, 1994[84]	USA	Cohort (population-based)	Black:285 White:3,144	1984-1990	NR	birth weight of <2500 grams	6
Ananth, 1995b[9]	USA	Cohort (population-based)	Black:14,417 White:15,819	1988 and 1990	Chronic hypertension obtained from medical records, no further details provided	birth weight of <2500 grams‡	8
Lydakis, 1998[85]	UK	Cohort (hospital-based)	Black:79 White:64	1980 to 1997	Hypertension (DBP ≥110 mmHg OR DBP >90 mmHg on two or more occasions ≥4 h apart) at the first booking visit before the 20 weeks' gestation in the absence of trophoblastic disease, OR hypertension at any stage of pregnancy that continued for more than 6 weeks after delivery	birth weight of <2000 grams	6
Graham, 2007[56]	USA	Cohort (population-based)	Black:91,718 White:111,213	1999 to 2003	Hypertension diagnosed before pregnancy	birth weight of <2500 grams	7
Odell, 2006[86]	USA	Population-based (Black women only)	Black:12,258 White: None	1996 to 2000	History of chronic hypertension diagnosed using ICD 9 codes	birth weight of <2500 grams	7

‡ We combined the ORs for birthweight < 1,499 g and birthweight (1,500-2,499 g).

Table S19: Characteristics of studies for pre-eclampsia outcome

Author, year published	*Country*	*Design*	*Sample size*	*Study duration*	*Definition of exposure*	*Comparative group*	*Definition of outcome*	*Newcastle-Ottawa grade*
Mabie, 1986[112]†	USA	Cohort (hospital-based)	169 pregnancies in 156 women	1980 to 1984	Women with CH who were on antihypertensive treatment	Untreated women with CH	Superimposed preeclampsia: worsening hypertension (30 mmHg SBP or 15 mmHg DBP) plus either nondependent edema or proteinuria of +1 or greater by dipstick.	6
Bayliss, 2002[109]‡	UK	Cohort (hospital-based)	491 pregnancies	1980 to 1999	Women with CH who were on antihypertensive treatment	Untreated women with CH	The onset of significant levels of proteinuria after 20 weeks gestation	6
Orbach, 2013[35]	Israel	Cohort (population- based)	98,253 births	1998 to 2008	Women with CH who were on antihypertensive treatment (methyldopa or atenolol) dispensed during the 1st trimester	Untreated normotensive women	Proteinuria diagnosed using ICD-9 codes	8
Rezk, 2016[110]	Egypt	Cohort (hospital-based)	222 women	2012 to 2016	Women with CH who were taking Methyldopa	Untreated women with CH	Superimposed preeclampsia: a new onset proteinuria with 0.3 g of protein or more in a 24-h urine specimen after 20 weeks' gestation), eclampsia (generalized convulsions)	4
Nzelu, 2018[111]	UK	Cohort (hospital-based)	419	2011 to 2016	women with CH on antihypertensive treatment	Untreated women with CH	Superimposed pre-eclampsia: hypertension, with at least 1 of the following problems: renal involvement (proteinuria 300 mg/24 h and/or creatinine 90 mmol/L or 1 mg/dL), liver impairment (transaminases >70 IU/L), neurologic complications (eg, eclampsia), thrombocytopenia (platelet count <150,000/mL).	7

Youngstrom, 2018[45]	USA	Cohort (hospital-based)	1,094 mother-infant pairs	2000 to 2014	women with CH on antihypertensive treatment	Untreated normotensive women	BP ≥140/90 with either proteinuria (protein excretion ≥300 mg in 24 hours or protein-to-creatinine ratio≥0.3), thrombocytopenia (less than 100,000/mL), transaminases (aspartate aminotransferase > twice the upper limit of normal), or elevated creatinine≥1.2 mg/dL	8
Mito, 2019[114§]	Japan	Cohort (population-based)	231 women	2008 to 2016	women with CH on antihypertensive treatment at the first trimester	Untreated women with CH	Superimposed pre-eclampsia diagnosed if a woman developed new-onset proteinuria in the with a rise in blood pressure or a sudden increase in pre-existing proteinuria.	7

CH: Chronic hypertension; BP: blood pressure. †The raw data for this study include women on methyldopa, other monotherapy, or multiple drug treatment vs. untreated women. ‡The odds ratios of this study were combined for different agents. §The raw data for this study include women on amlodipine or other antihypertensive drug treatment vs. untreated women

Table S20: Characteristics of studies for cesarean section (CS) outcome

Author, year published	*Country (ies)*	*Design*	*Sample size*	*Study duration*	*Definition of exposure*	*Comparative group*	*Definition of outcome*	*Newcastle-Ottawa grade*
Rezk, 2016[110]	Egypt	Cohort (hospital-based)	222 women	2012 to 2016	Women with CH who were taking Methyldopa	Untreated women with CH	Caesarean section (not specified)	4
Hoeltzenbei, 2017[107‡]	Germany	Cohort	787 pregnancies	2000 to 2014	pregnancies with methyldopa exposure at least during the first trimester, but no longer than 20 weeks' gestation	Untreated normotensive women	Caesarean section (not specified)	5

CH: Chronic hypertension

Table S21: Characteristics of studies for miscarriage outcome

Author, year published	*Country (ies)*	*Design*	*Sample size*	*Study duration*	*Definition of exposure*	*Comparative group*	*Definition of outcome*	*Newcastle -Ottawa grade*
Bayliss, 2002[109]	UK	Cohort (hospital-based)	491 pregnancies	1980 to 1999	Women with CH who were on antihypertensive treatment	Untreated women with CH	miscarriages	6
Hoeltzenbei, 2017[107]	Germany	Cohort	787 pregnancies	2000 to 2014	pregnancies with methyldopa exposure at least during the first trimester, but no longer than 20 weeks' gestation	Untreated normotensive women	Spontaneous pregnancy loss of a fetus <500 g or in case of unknown weight <24 completed weeks after last menstrual period	5

CH: Chronic hypertension

Table S22: Characteristics of studies for stillbirth outcome

Author, year published	*Country (ies)*	*Design*	*Sample size*	*Study duration*	*Definition of exposure*	*Comparative group*	*Definition of outcome*	*Newcastle -Ottawa grade*
Bayliss, 2002[109]	UK	Cohort (hospital-based)	491 pregnancies	1980 to 1999	Women with CH who were on antihypertensive treatment	Untreated women with CH	Stillbirth	6
Hoeltzenbei, 2017[107]	Germany	Cohort	787 pregnancies	2000 to 2014	pregnancies with methyldopa exposure at least during the first trimester, but no longer than 20 weeks' gestation	Untreated normotensive women	Stillbirth	5
Rezk, 2016[110]	Egypt	Cohort (hospital-based)	222 women	2012 to 2016	Women with CH who were taking Methyldopa	Untreated women with CH	Intrauterine fetal death	4
Youngstrom, 2018[45]	USA	Cohort (hospital-based)	1,094 mother-infant pairs	2000 to 2014	women with CH on antihypertensive treatment	Untreated normotensive women	Stillbirth	8

CH: Chronic hypertension

Table S23a: Characteristics of studies for Preterm birth outcome

Author, year published	*Country*	*Design*	*Sample size*	*Study duration*	*Definition of exposure*	*Comparative group*	*Definition of outcome*	*Newcastle -Ottawa grade*
Ray, 2001[108]†	Canada	Cohort (hospital-based)	583 mother-infant pairs	1986 to 1995	women with CH on antihypertensive treatment	Untreated women with CH	<37 weeks' gestation	6
Lennestål, 2009[105]	Sweden	Cohort (population-based)	1,032,094 pregnancies	1995 to 2006	Women who reported using antihypertensive treatment in early pregnancy, and with a delivery diagnosis of CH for women who were on beta-blocking drug	Untreated normotensive women	<37 weeks' gestation	8
Banhidy, 2010[106]	Hungary	Case control (population based)	36,155 births	1980 to 1996	Women with CH on antihypertensive treatment	Untreated normotensive women	<37 weeks' gestation	6
Su, 2013[60]§	Taiwan	Cohort (population-based)	2,727 mother-infant pairs	2005	women with CH on antihypertensive treatment	Untreated women with CH	<37 weeks' gestation	8
Orbach, 2013[35]	Israel	Cohort (population-based)	98,253 births	1998 to 2008	Women with CH who were on antihypertensive treatment (methyldopa or atenolol) dispensed during the 1st trimester	Untreated normotensive women	<37 weeks' gestation	8
Rezk, 2016[110]	Egypt	Cohort (hospital-based)	222 women	2012 to 2016	Women with CH who were taking methyldopa	Untreated women with CH	<37 weeks' gestation	4
Hoeltzenbei, 2017[107]	Germany	Cohort	787 pregnancies	2000 to 2014	pregnancies with methyldopa exposure at least during the first trimester, but no longer than 20 weeks' gestation	Untreated normotensive women	<37 weeks' gestation	5

Youngstrom, 2018[45]	USA	Cohort (hospital-based)	1,094 mother-infant pairs	2000 to 2014	women with CH on antihypertensive treatment	Untreated normotensive women	<37 weeks' gestation	8
Mito, 2019[114]‡	Japan	Cohort (population-based)	231 women	2008 to 2016	women with CH on antihypertensive treatment at the first trimester	Untreated women with CH	<37 weeks' gestation	7

CH: Chronic hypertension.

†We combined odds ratios from this study for women using beta-blockers or other agents.

§The odds ratios of these studies were combined for different agents.

‡The raw data for this study include women on amlodipine or other antihypertensive drug treatment vs. untreated women

Table S23b: Characteristics for preterm birth outcome: (exposed to beta-blockers vs. untreated)

Author, year published	*Country*	*Design*	*Sample size*	*Study duration*	*Definition of exposure*	*Comparative group*	*Definition of outcome*	*Newcastle -Ottawa grade*
Ray, 2001[108]	Canada	Cohort (hospital-based)	391mother-infant pairs	1986 to 1995	women with CH on β-blocker treatment	Untreated women with CH	<37 weeks' gestation	6
Su, 2013[60]	Taiwan	Cohort (population-based)	1,420 mother-infant pairs	2005	Pregnant women with CH who were exposed to β-blockers	Untreated women with CH	<37 weeks' gestation	8
Orbach, 2013[35]	Israel	Cohort (population-based)	97,927 births	1998 to 2008	Pregnant women with CH who were exposed to atenolol	Untreated normotensive women	<37 weeks' gestation	8

Table S23c: Characteristics for Preterm birth outcome: (exposed to RAS vs. other agents)

Author, year published	*Country*	*Design*	*Sample size*	*Study duration*	*Definition of exposure*	*Comparative group*	*Definition of outcome*	*Newcastle -Ottawa grade*
Ahmed, 2018[116]	Australia	Cohort (population-based)	456 pregnancies	2005 and 2012	Pregnancies with CH on ARBs exposure at first trimester	Pregnant women on methyldopa	<37 weeks' gestation	7

CH: Chronic hypertension; ARB: angiotensin-receptor blockers

Table S24a: Characteristics of studies for small for gestational age (SGA) outcome

Author, year published	*Country*	*Design*	*Sample size*	*Study duration*	*Definition of exposure*	*Comparative group*	*Definition of outcome*	*Newcastle -Ottawa grade*
Mabie, 1986[112]†	USA	Cohort (hospital-based)	169 pregnancies in 156 women	1980 to 1984	Women with CH who were on antihypertensive treatment	Untreated women with CH	Birthweight <10th percentile	6
Ray, 2001[108]*	Canada	Cohort (hospital-based)	583 mother-infant pairs	1986 to 1995	women with CH on antihypertensive treatment	Untreated women with CH	Birthweight <10th percentile	6
Bayliss, 2002[109]*	UK	Cohort (hospital-based)	491 pregnancies	1980 to 1999	Women with CH who were on antihypertensive treatment	Untreated women with CH	Birthweight <10th percentile	6
Lennestål, 2009[105]	Sweden	Cohort (population-based)	1,032,094 pregnancies	1995 to 2006	Women who reported using antihypertensive treatment in early pregnancy, and with a delivery diagnosis of chronic hypertension for women who were on beta-blocking drug	Untreated normotensive women	Birthweight < -2SD	8
Su, 2013[60]*	Taiwan	Cohort (population-based)	2,727 mother-infant pairs	2005	women with CH on antihypertensive treatment	Untreated women with CH	Birthweight <10th percentile	8
Orbach, 2013[35]	Israel	Cohort (population-based)	98,253 births	1998 to 2008	Women with CH who were on antihypertensive treatment (methyldopa or atenolol) dispensed during the 1st trimester	Untreated normotensive women	SGA diagnosed using ICD-9	8
Rezk, 2016[110]	Egypt	Cohort (hospital-based)	222 women	2012 to 2016	Women with CH who were taking Methyldopa	Untreated women with CH	Birthweight <10th percentile	4
Nzelu, 2018[111]	UK	Cohort (hospital-based)	419	2011 to 2016	women with CH on antihypertensive treatment	Untreated women with CH	Birthweight <5th percentile	7

Fisher, 2018[117]	USA	Cohort (population-based)	4,282 mother-infant pairs	2006 to 2011	Women with CH on antihypertensive treatment	Untreated normotensive women	Birthweight <10th percentile	6
Youngstrom, 2018[45]	USA	Cohort (hospital-based)	1,094 mother-infant pairs	2000 to 2014	women with CH on antihypertensive treatment	Untreated normotensive women	Birthweight <10th percentile	8

CH: Chronic hypertension . * We combined odds ratios from these studies were combined for different agents. †The raw data for this study include women on methyldopa, other monotherapy, or multiple drug treatment vs. untreated women.

Table S24b: Characteristics of studies for SGA outcome: (beta blockers vs. untreated women)

Author, year published	*Country*	*Design*	*Sample size*	*Study duration*	*Definition of exposure*	*Comparative group*	*Definition of outcome*	*Newcastle -Ottawa grade*
Ray, 2001[108]	Canada	Cohort (hospital-based)	391 mother-infant pairs	1986 to 1995	Pregnant women with CH who were exposed to β-blockers	Untreated women with CH	Birth weight<10th percentile	6
Bayliss, 2002[109]	UK	Cohort (hospital-based)	229 pregnancies	1980 to 1999	Pregnant women with CH who were exposed to atenolol<15 weeks' gestation	Untreated women with CH	Birth weight<10th percentile	6
Su, 2013[60]	Taiwan	Cohort (population-based)	1,420 mother-infant pairs	2005	Pregnant women with CH who were exposed to β-blockers	Untreated women with CH	Birth weight<10th percentile	8
Orbach, 2013[35]	Israel	Cohort (population-based)	97,927 births	1998 to 2008	Pregnant women with CH who were exposed to atenolol	Untreated normotensive women	SGA diagnosed using ICD-9	8

CH: Chronic hypertension; β-blockers: beta blockers

Table S24c: Characteristics of studies for SGA outcome: (single agent/multiple agents vs. untreated women)

Author, year published	*Country*	*Design*	*Sample size*	*Study duration*	*Definition of exposure*	*Comparative group*	*Definition of outcome*	*Newcastle -Ottawa grade*
Ray, 2001[108]	Canada	Cohort (hospital-based)	500 mother-infant pairs (untreated. n=247, sing. n=144 multi. n=109)	1986 to 1995	women with CH who were on single agent (βB), or on multiple agents	Untreated women with CH	Birthweight<10th percentile	6
Bayliss, 2002[109]	UK	Cohort (hospital-based)	268 pregnancies (sing. n=229, multi. n=243)	1980 to 1999	Women with CH who were on single agent (atenolol), or on multiple agents	Untreated women with CH	Birthweight<10th percentile	6
Su, 2013[60]	Taiwan	Cohort (population-based)	1,543 mother-infant pairs (untreated n=1,006, sing. n=144, multi. n=123)	2005	women with CH who were on single agent (βB), or on multiple agents	Untreated women with CH	Birthweight <10th percentile	8

CH: Chronic hypertension; βB: beta-blockers

Table S24d: Characteristics of studies for SGA outcome: (centrally acting antiadrenergic vs. untreated women)

Author, year published	*Country*	*Design*	*Sample size*	*Study duration*	*Definition of exposure*	*Comparative group*	*Definition of outcome*	*Newcastle -Ottawa grade*
Mabie, 1986[112]	USA	Cohort (hospital-based)	136 pregnancies	1980 to 1984	Pregnant women who were exposed to methyldopa	Untreated women with CH	Birthweight<10th percentile	6
Su, 2013[60]	Taiwan	Cohort (population-based)	1,187 mother-infant pairs	2005	Pregnant women who were exposed to centrally acting antiadrenergic	Untreated women with CH	Birthweight<10th percentile	8
Orbach, 2013[35]	Israel	Cohort (population-based)	98,160 births	1998 to 2008	Pregnant women who were exposed to methyldopa	Untreated normotensive women	SGA diagnosed using ICD-9	8
Rezk, 2016[110]	Egypt	Cohort (hospital-based)	222 women	2012 to 2016	Pregnant women who were exposed to methyldopa	Untreated women with CH	Birthweight<10th percentile	4

CH: Chronic hypertension.

Table S24e: Characteristics of studies for SGA outcome: (methyldopa vs other agents)

Author, year published	*Country*	*Design*	*Sample size*	*Study duration*	*Definition of exposure*	*Comparative group*	*Definition of outcome*	*Newcastle -Ottawa grade*
Mabie, 1986[112]	USA	Cohort (hospital-based)	64 pregnancies	1980 to 1984	Pregnant women with CH who were exposed to methyldopa	Pregnant women with CH on hydrochlorothiazide	Birthweight<10th percentile	6
Su, 2013[60]	Taiwan	Cohort (population-based)	595 mother-infant pairs	2005	Pregnant women who were exposed to centrally acting antiadrenergic	Pregnant women with CH on β-blockers	Birthweight<10th percentile	8
Orbach, 2013[35]	Israel	Cohort (population-based)	447 births	1998 to 2008	Pregnant women with CH who were exposed to methyldopa	Pregnant women with CH who were exposed to atenolol	SGA diagnosed using ICD-9	8
Xie,2014[115]	Canada	Cohort (population-based)	628 Women with CH	1980 to 1987 or 1990 to 2005	Pregnant women with CH who were exposed to methyldopa	Pregnant women with CH on β-blockers	Birthweight<10th percentile	7
Ahmed, 2018[116]	Australia	Cohort (population-based)	456 pregnancies	2005 and 2012	Pregnant women with CH who were exposed to methyldopa	Pregnancies with CH on ARBs exposure at first trimester	Birthweight<10th percentile	7

CH: Chronic hypertension; ARB: angiotensin-receptor blockers

Table S24f: Characteristics of studies for SGA outcome: (beta blockers vs. methyldopa)

Author, year published	*Country*	*Design*	*Sample size*	*Study duration*	*Definition of exposure*	*Comparative group*	*Definition of outcome*	*Newcastle -Ottawa grade*
Su, 2013[60]	Taiwan	Cohort (population-based)	595 mother-infant pairs	2005	Pregnant women with CH on β-blockers	Pregnant women who were exposed to centrally acting antiadrenergic	Birthweight<10th percentile	8
Orbach, 2013[35]	Israel	Cohort (population-based)	447 births	1998 to 2008	Pregnant women with CH who were exposed to atenolol	Pregnant women with CH who were exposed to methyldopa	SGA diagnosed using ICD-9	8
Xie,2014[115]	Canada	Cohort (population-based)	628 Women with CH	1980 to 1987 or 1990 to 2005	Pregnant women with CH on β-blockers	Pregnant women with CH who were exposed to methyldopa	Birthweight<10th percentile	7

CH: Chronic hypertension

Table S25: Characteristics of studies for low birth weight (LBW) outcome

Author, year published	*Country*	*Design*	*Sample size*	*Study duration*	*Definition of exposure*	*Comparative group*	*Definition of outcome*	*Newcastle-Ottawa grade*
Lennestål, 2009[105]	Sweden	Cohort (population-based)	1,032,094 pregnancies	1995 to 2006	Women who reported using antihypertensive treatment in early pregnancy, and with a delivery diagnosis of chronic hypertension for women who were on beta-blocking drug	Untreated normotensive women	Birthweight < 2,500g	8
Banhidy, 2010[106]	Hungary	Case control (population based)	36,155 births	1980 to 1996	Women with CH on antihypertensive treatment	Untreated normotensive women	Birthweight < 2,500g	6
Su, 2013[60]§	Taiwan	Cohort (population-based)	2,727 mother-infant pairs	2005	women with CH on antihypertensive treatment	Untreated women with CH	Birthweight < 2,500g	8
Orbach, 2013[35]	Israel	Cohort (population-based)	98,253 births	1998 to 2008	Women with CH who were on antihypertensive treatment (methyldopa or atenolol) dispensed during the 1st trimester	Untreated normotensive women	Birthweight < 2,500g	8
Mito, 2019[114]†	Japan	Cohort (population-based)	231 women	2008 to 2016	women with CH on antihypertensive treatment at the first trimester	Untreated women with CH	Birthweight < 2,500g	7

CH: Chronic hypertension.

§The ORs of these studies were combined for different agents.†The raw data for this study include women on amlodipine or other antihypertensive drug treatment vs. untreated women.

Table S26: Characteristics of studies for neonatal intensive care unit (NICU) admission outcome

Author, year published	*Country*	*Design*	*Sample size*	*Study duration*	*Definition of exposure*	*Comparative group*	*Definition of outcome*	*Newcastle -Ottawa grade*
Rezk, 2016[110]	Egypt	Cohort (hospital-based)	222 women	2012 to 2016	Women with CH who were taking Methyldopa	Untreated women with CH	Admission to NICU	4
Helou, 2017[113]	Australia	Cohort (hospital-based)	49 women	2010	Women with CH on antihypertensive treatment	Untreated women with CH	Admission to NICU or SCN	6

CH: Chronic hypertension; SCN: Special care nursery.

Table S27: Characteristics of studies for perinatal death outcome

Author, year published	*Country*	*Design*	*Sample size*	*Study duration*	*Definition of exposure*	*Comparative group*	*Definition of outcome*	*Newcastle -Ottawa grade*
Mabie, 1986[112]†	USA	Cohort (hospital-based)	169 pregnancies in 156 women	1980 to 1984	Women with CH who were on antihypertensive treatment	Untreated women with CH	Not reported	6
Ray, 2001[108]*	Canada	Cohort (hospital-based)	1,948 mother-infant pairs	1986 to 1995	women with CH or other HDP on antihypertensive treatment	Untreated women with CH or HDP	Perinatal death after 20 weeks gestation and up to 30 days after birth	6
Orbach, 2013[35]	Israel	Cohort (population- based)	98,253 births	1998 to 2008	Women with CH who were on antihypertensive treatment (methyldopa or atenolol) dispensed during the first trimester	Untreated normotensive women	Not reported	8
Youngstrom, 2018[45]	USA	Cohort (hospital-based)	1,094 mother-infant pairs	2000 to 2014	women with CH on antihypertensive treatment	Untreated normotensive women	Stillbirth and neonatal death	8

CH: chronic hypertension.

†The raw data for this study include women on methyldopa, other monotherapy, or multiple drug treatment vs. untreated women.

*We combined odds ratios from this study for women using beta-blockers or other agents

Figure S1a: Forest plot of crude estimates of the association between chronic hypertension and PE

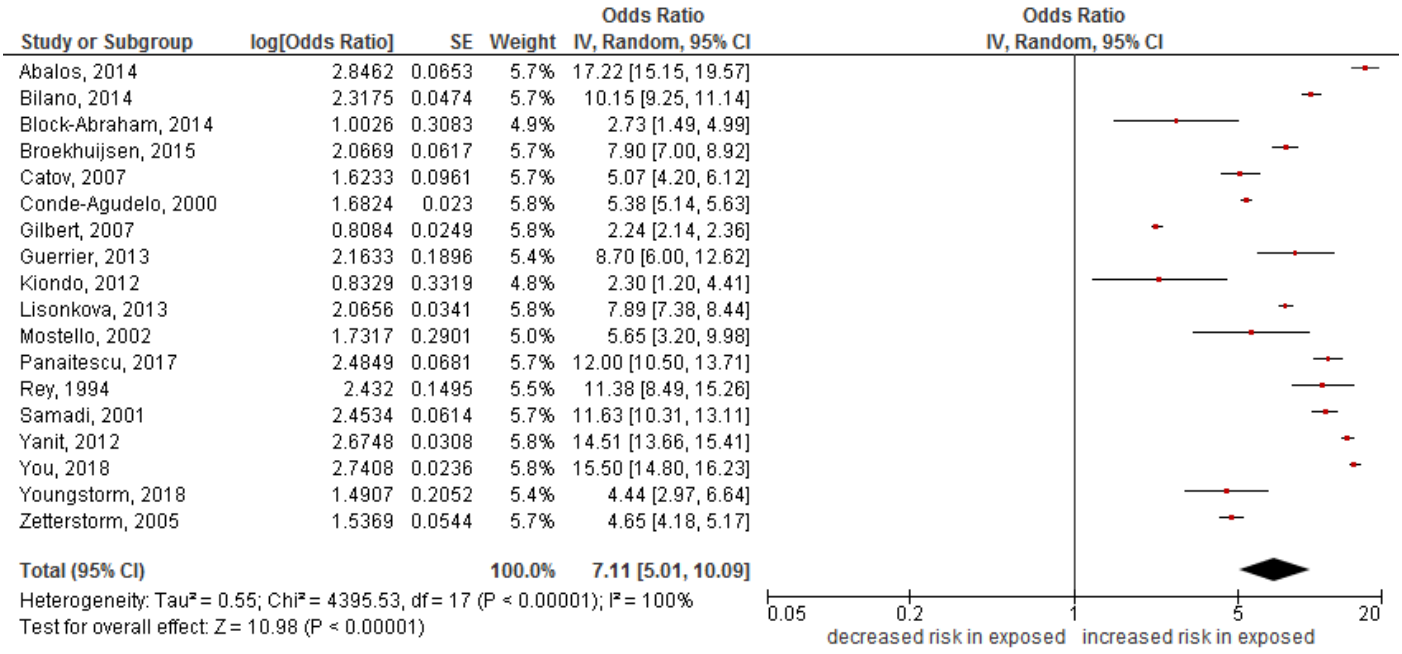


Figure S1b: Funnel plot for adjusted estimates of PE (chronic hypertension versus normotensive)

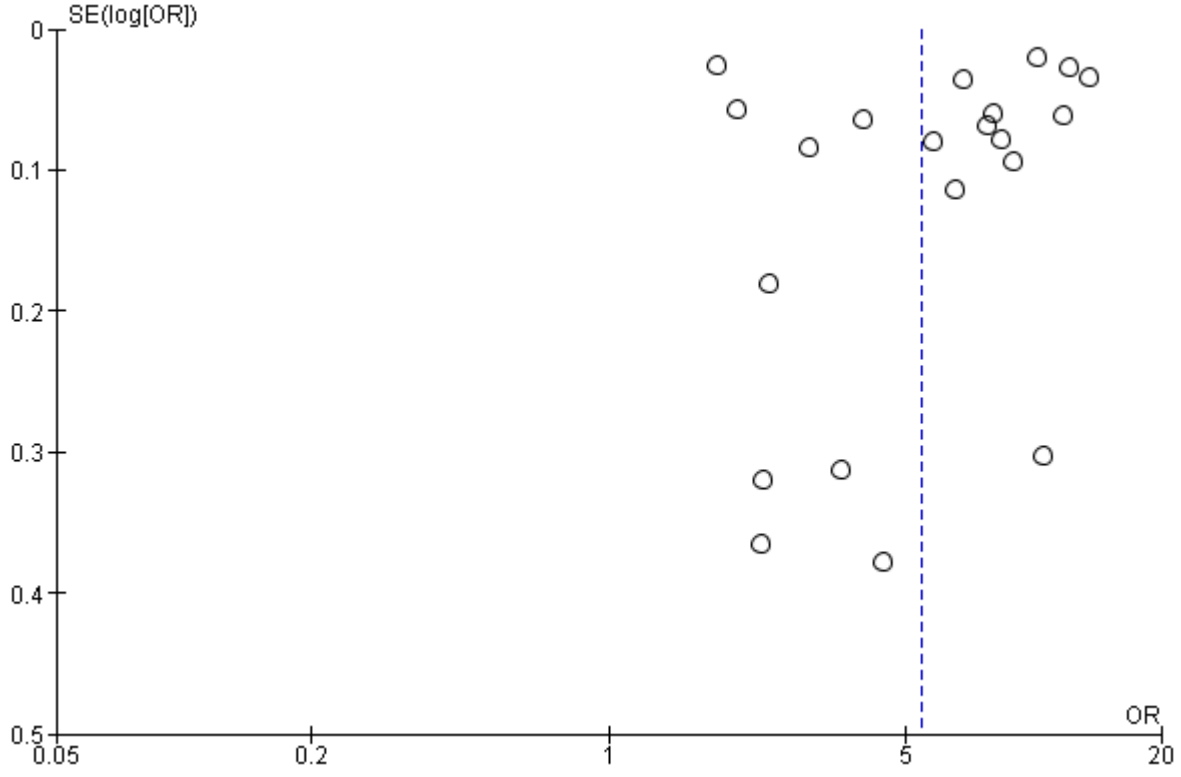


Figure S2a: Forest plot of crude estimates of the association between chronic hypertension and HEELP syndrome

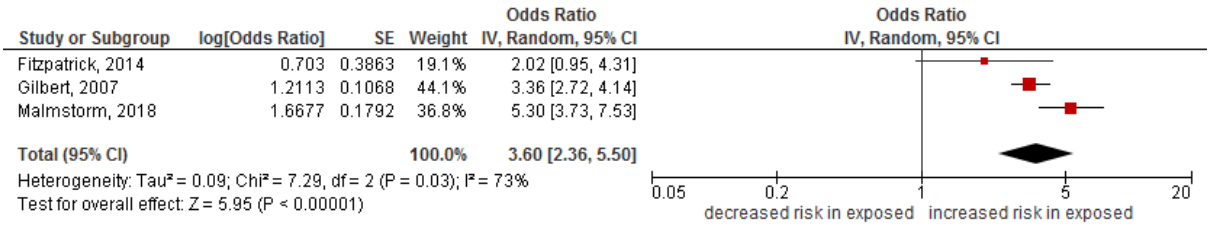


Figure S2b: Forest plot of adjusted estimates of the association between chronic hypertension and HEELP syndrome

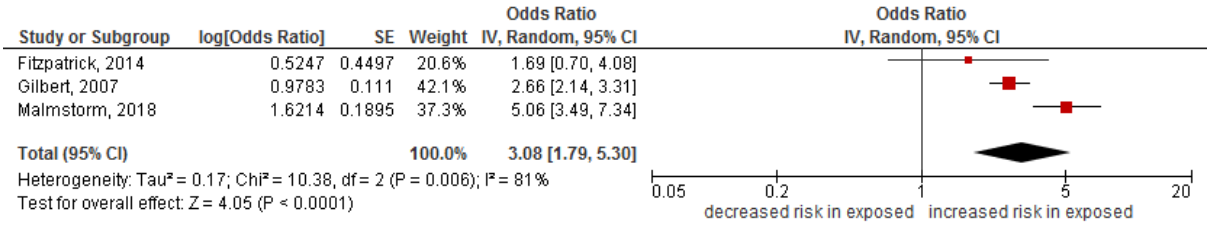


Figure S3a: Forest plot of crude estimates of the association between chronic hypertension and CS

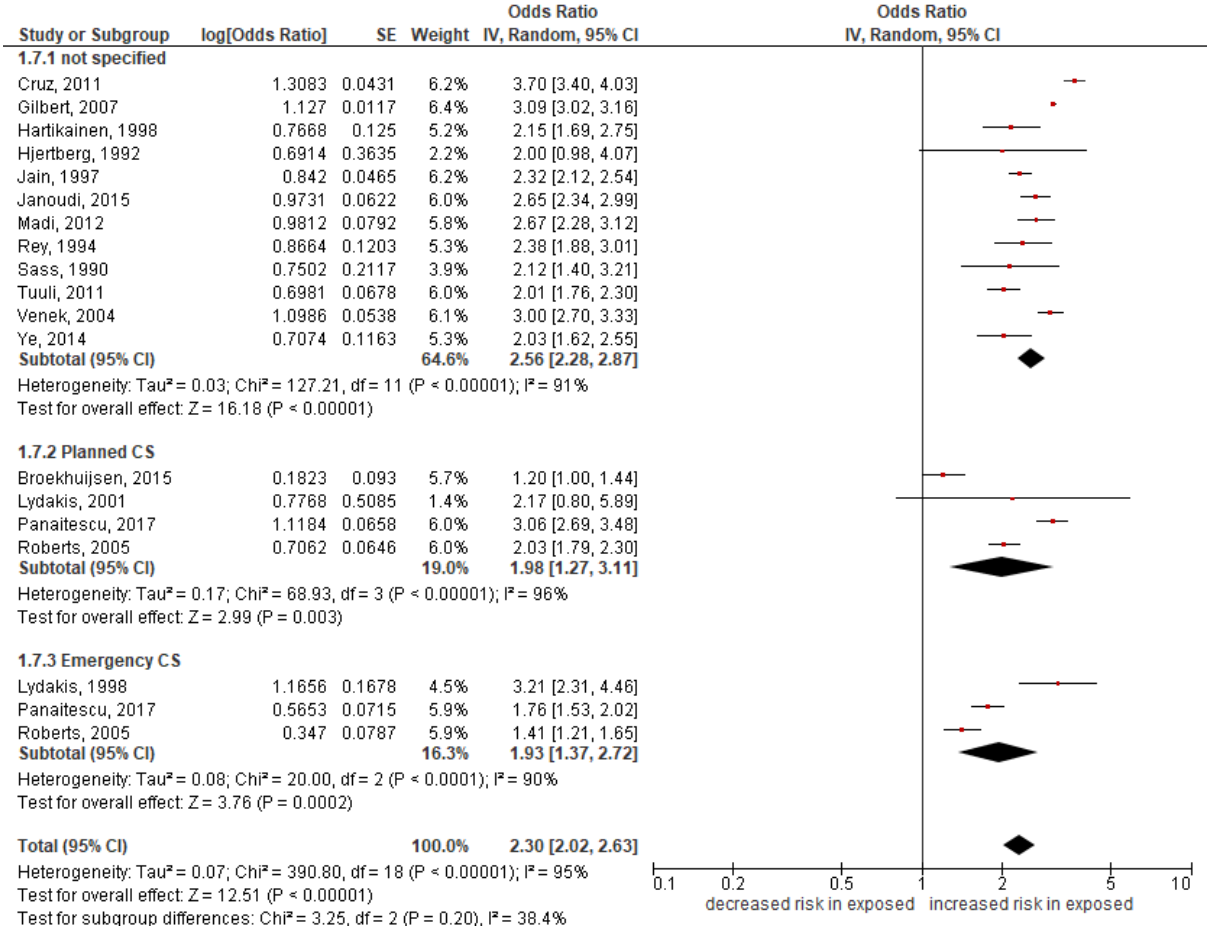


Figure S3b: Forest plot of adjusted estimates of the association between chronic hypertension and CS

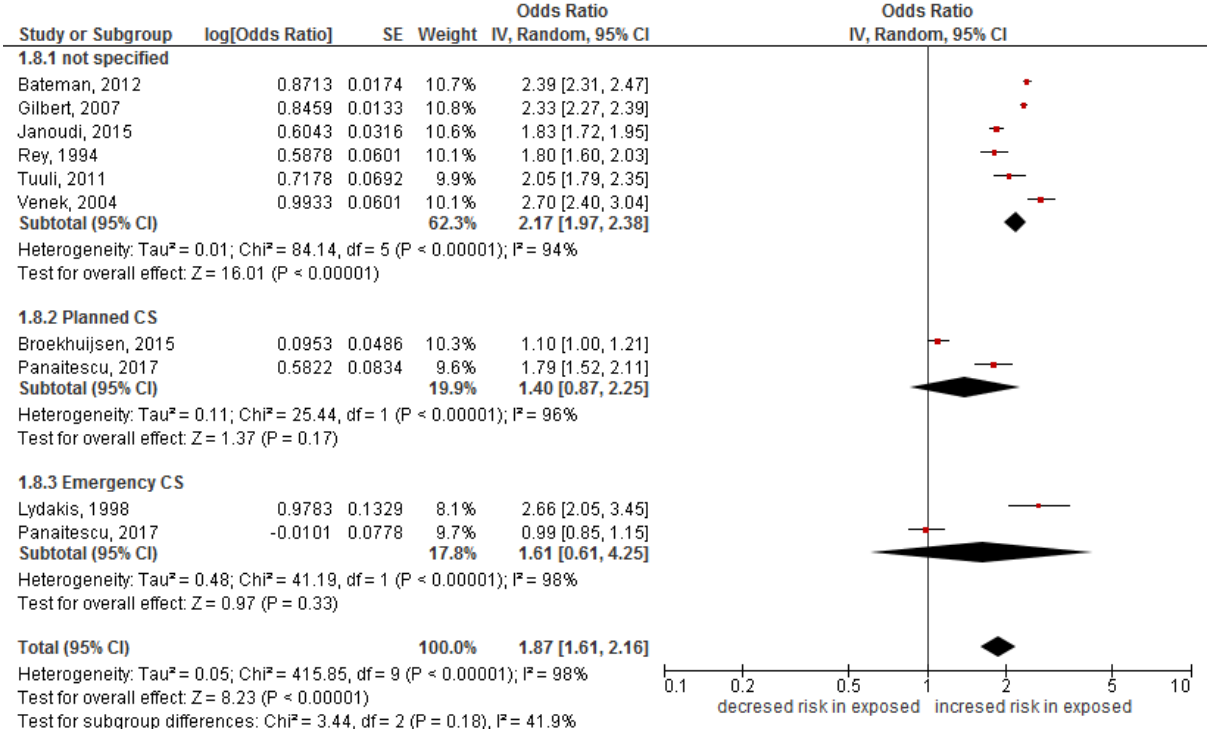


Figure S3c: Funnel plot for adjusted estimates of CS (chronic hypertension versus normotensive)

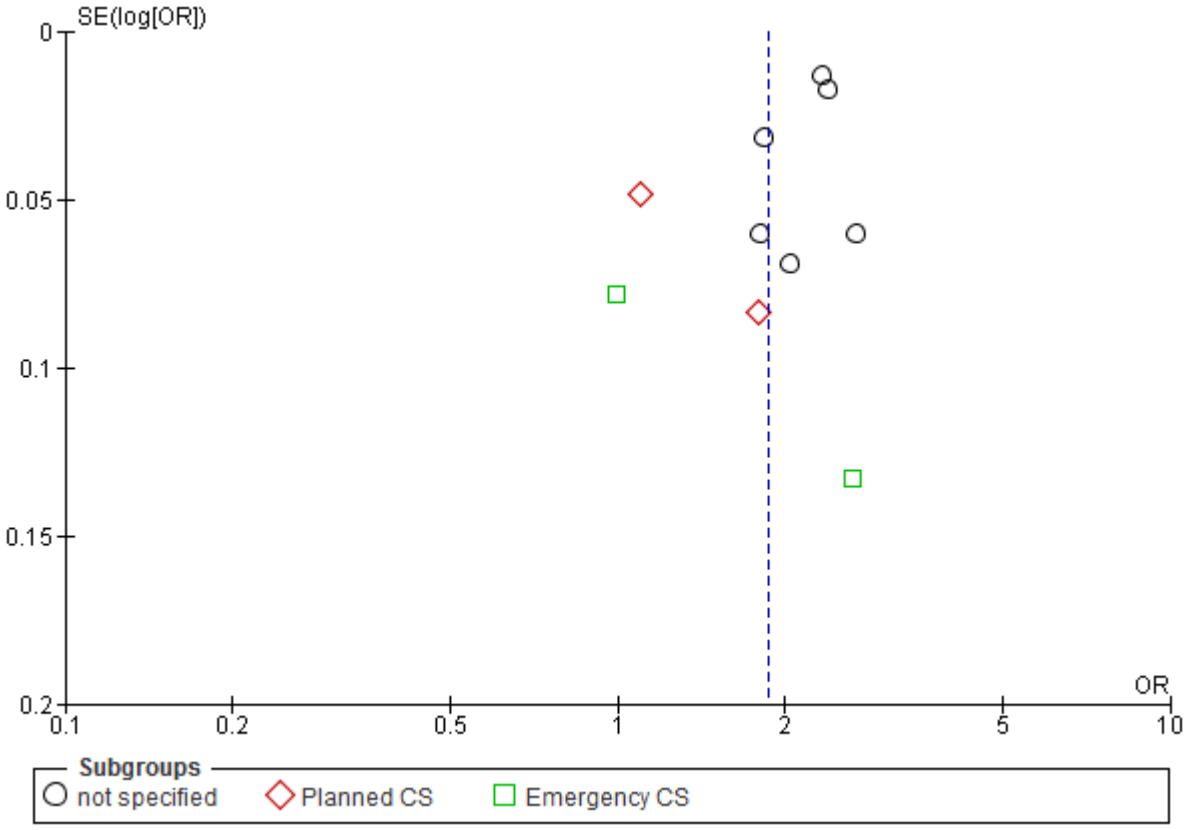


Figure S4a: Forest plot of crude estimates of the association between chronic hypertension and PPH

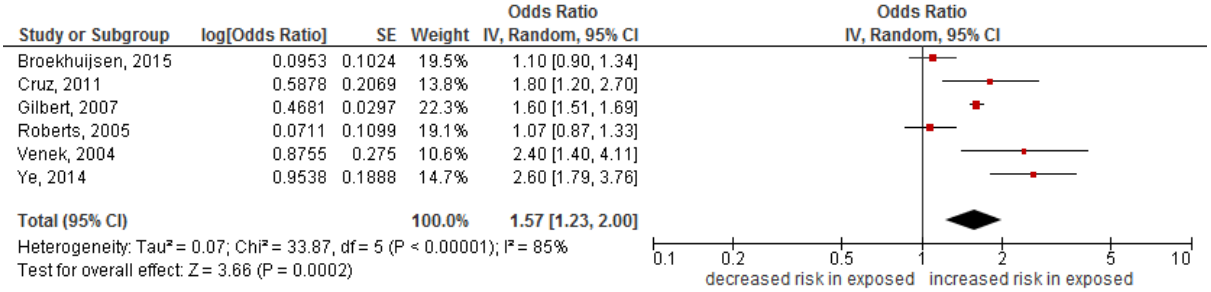


Figure S4b: Forest plot of adjusted estimates of the association between chronic hypertension and PPH

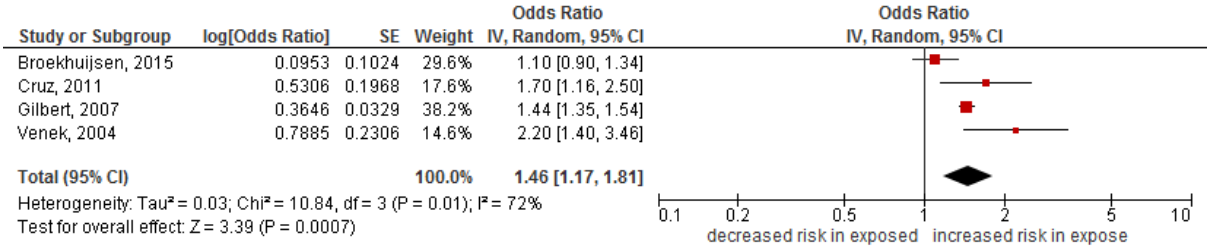


Figure S5: Forest plot of crude estimates of the association between chronic hypertension and maternal mortality

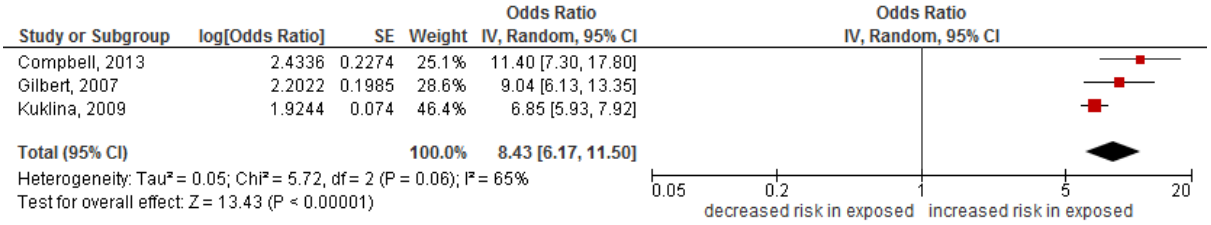


Figure S6a: Forest plot of crude estimates of the association between chronic hypertension and stillbirth

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Aagord-Tittery, 2006	1.2442	0.3551	2.0%	3.47 [1.73, 6.96]
Ahmed, 2012	0.8074	0.111	7.6%	2.24 [1.80, 2.79]
Allen, 2004	1.1632	0.266	3.1%	3.20 [1.90, 5.39]
Ananth, 1995	1.1741	0.12	7.2%	3.24 [2.56, 4.09]
Canterino, 2004	1.2981	0.031	10.6%	3.66 [3.45, 3.89]
Conde-Agudelo, 2000b	0.9859	0.0448	10.2%	2.68 [2.45, 2.93]
Gilbert, 2007	1.1878	0.0354	10.5%	3.28 [3.06, 3.52]
Lydakis, 1998	1.5602	0.3645	1.9%	4.76 [2.33, 9.72]
Madi, 2012	1.8358	0.3198	2.4%	6.27 [3.35, 11.74]
Panaitescu, 2017	1.3987	0.2203	4.0%	4.05 [2.63, 6.24]
Reddy, 2010	0.9858	0.1519	6.0%	2.68 [1.99, 3.61]
Roberts, 2005	0.8116	0.2325	3.7%	2.25 [1.43, 3.55]
Tuuli, 2011	0.8796	0.2154	4.1%	2.41 [1.58, 3.68]
Xiong, 2018	0.9026	0.0565	9.8%	2.47 [2.21, 2.75]
Yanit, 2012	0.9977	0.1518	6.0%	2.71 [2.01, 3.65]
Yerlikaya, 2016	1.5173	0.2205	4.0%	4.56 [2.96, 7.02]
Youngstorm, 2018	0.7575	0.4642	1.3%	2.13 [0.86, 5.30]
Zetterstorm, 2006	0.9959	0.1641	5.6%	2.71 [1.96, 3.73]
Total (95% CI)			**100.0%**	**3.00 [2.69, 3.35]**

Heterogeneity: Tau² = 0.03; Chi² = 83.53, df = 17 (P < 0.00001); I² = 80%
Test for overall effect: Z = 19.82 (P < 0.00001)

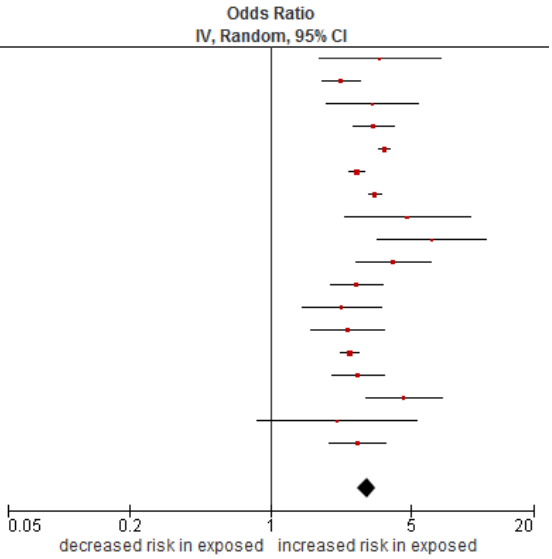


Figure S6b: Forest plot of adjusted estimates of the association between chronic hypertension and stillbirth

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Aagord-Tittery, 2006	1.2413	0.5665	0.2%	3.46 [1.14, 10.50]
Ahmed, 2012	0.7514	0.1097	4.0%	2.12 [1.71, 2.63]
Allen, 2004	1.1632	0.266	0.7%	3.20 [1.90, 5.39]
Ananth, 1995	1.0367	0.1221	3.2%	2.82 [2.22, 3.58]
Bateman, 2012	0.802	0.0505	18.9%	2.23 [2.02, 2.46]
Canterino, 2004	0.8587	0.0475	21.4%	2.36 [2.15, 2.59]
Conde-Agudelo, 2000b	0.8109	0.0678	10.5%	2.25 [1.97, 2.57]
Copper, 1994	0.5306	0.3189	0.5%	1.70 [0.91, 3.18]
Gilbert, 2007	0.8587	0.0428	26.4%	2.36 [2.17, 2.57]
Jain, 1997	1.0986	0.1582	1.9%	3.00 [2.20, 4.09]
Panaitescu, 2017	0.8671	0.2321	0.9%	2.38 [1.51, 3.75]
Reddy, 2010	0.6931	0.1468	2.2%	2.00 [1.50, 2.67]
Tuuli, 2011	0.6259	0.2221	1.0%	1.87 [1.21, 2.89]
Xiong, 2018	0.8416	0.11	4.0%	2.32 [1.87, 2.88]
Yanit, 2012	0.9163	0.1968	1.2%	2.50 [1.70, 3.68]
Yerlikaya, 2016	0.9632	0.2328	0.9%	2.62 [1.66, 4.13]
Youngstorm, 2018	0.6575	0.4007	0.3%	1.93 [0.88, 4.23]
Zetterstorm, 2006	0.7129	0.1637	1.8%	2.04 [1.48, 2.81]
Total (95% CI)			**100.0%**	**2.32 [2.22, 2.42]**

Heterogeneity: Tau² = 0.00; Chi² = 13.11, df = 17 (P = 0.73); I² = 0%
Test for overall effect: Z = 38.32 (P < 0.00001)

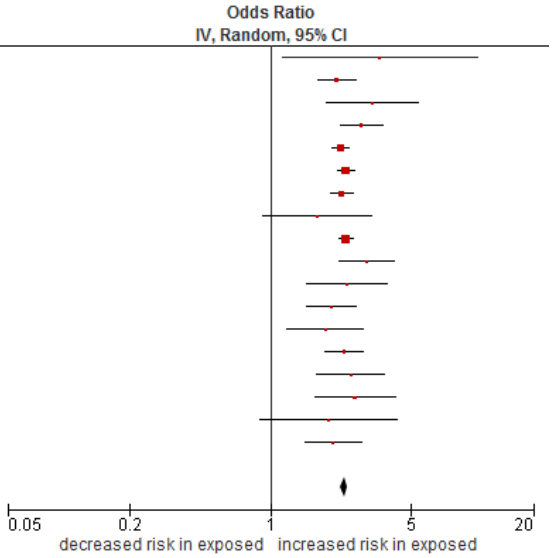


Figure S6c: Funnel plot for adjusted estimates of stillbirth (chronic hypertension versus normotensive)

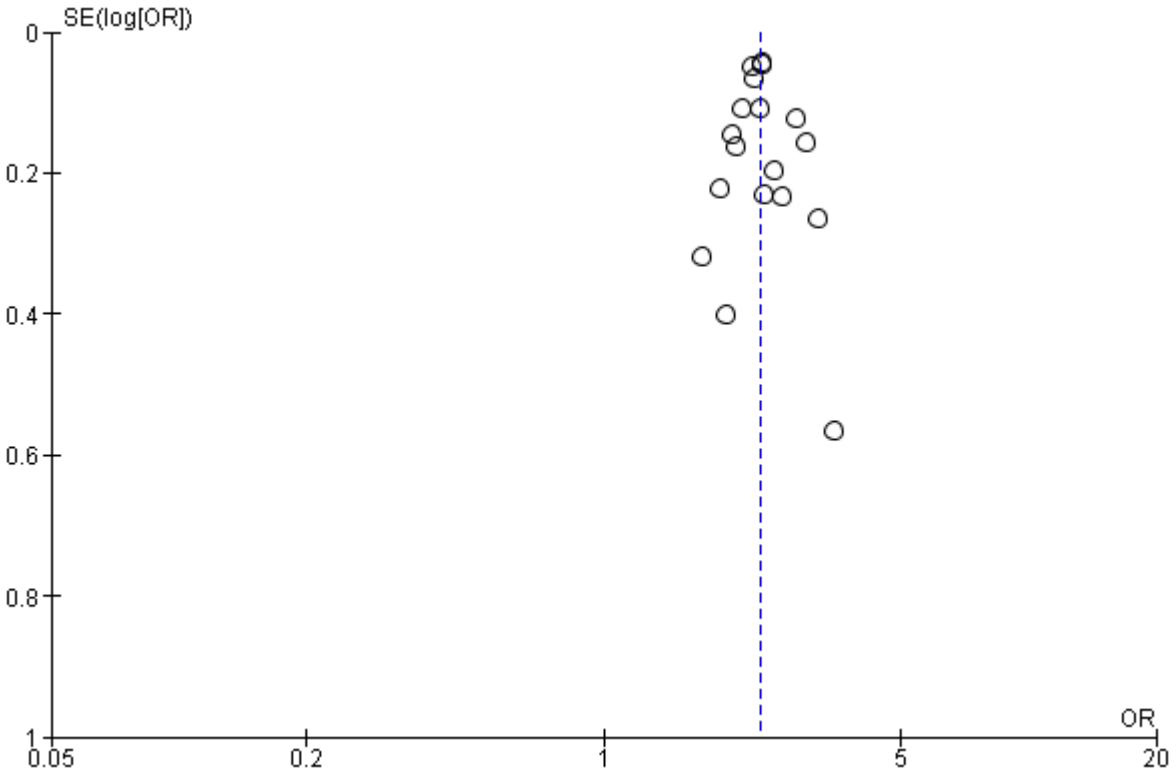


Figure S7a: Forest plot of crude estimates of the association between chronic hypertension and VPTB

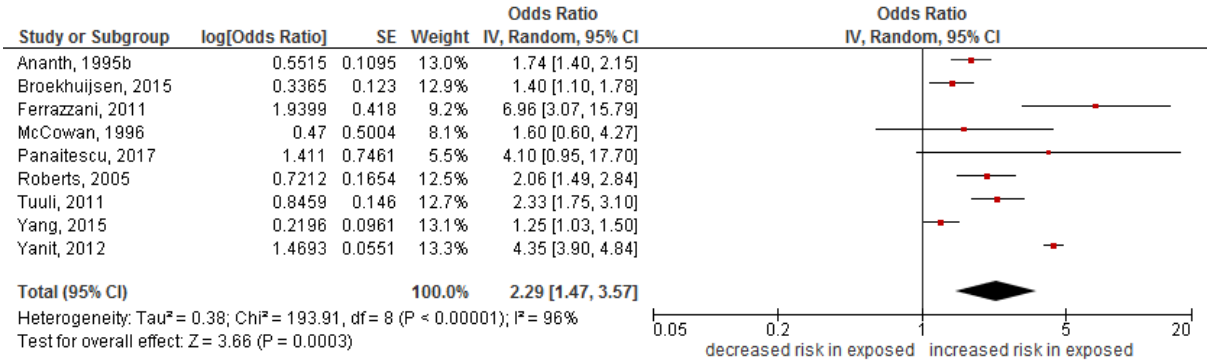


Figure S7b: Forest plot of adjusted estimates of the association between chronic hypertension and VPTB

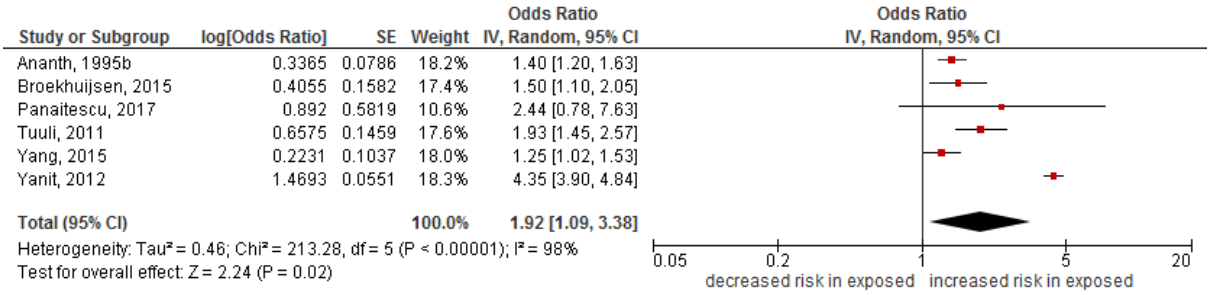


Figure S8a: Forest plot of crude estimates of the association between chronic hypertension and PTB

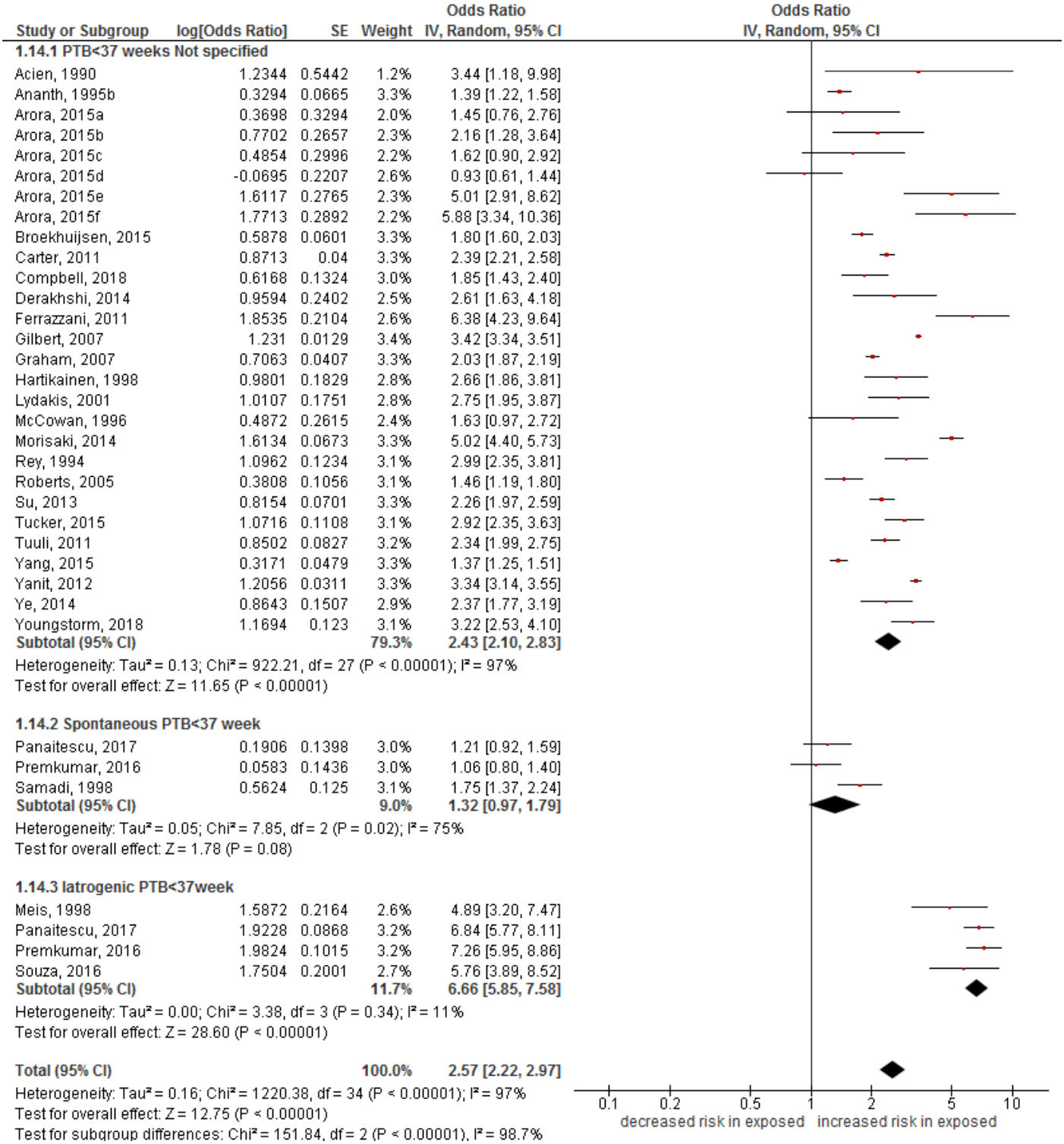


Figure S8b: Forest plot of adjusted estimates of the association between chronic hypertension and PTB

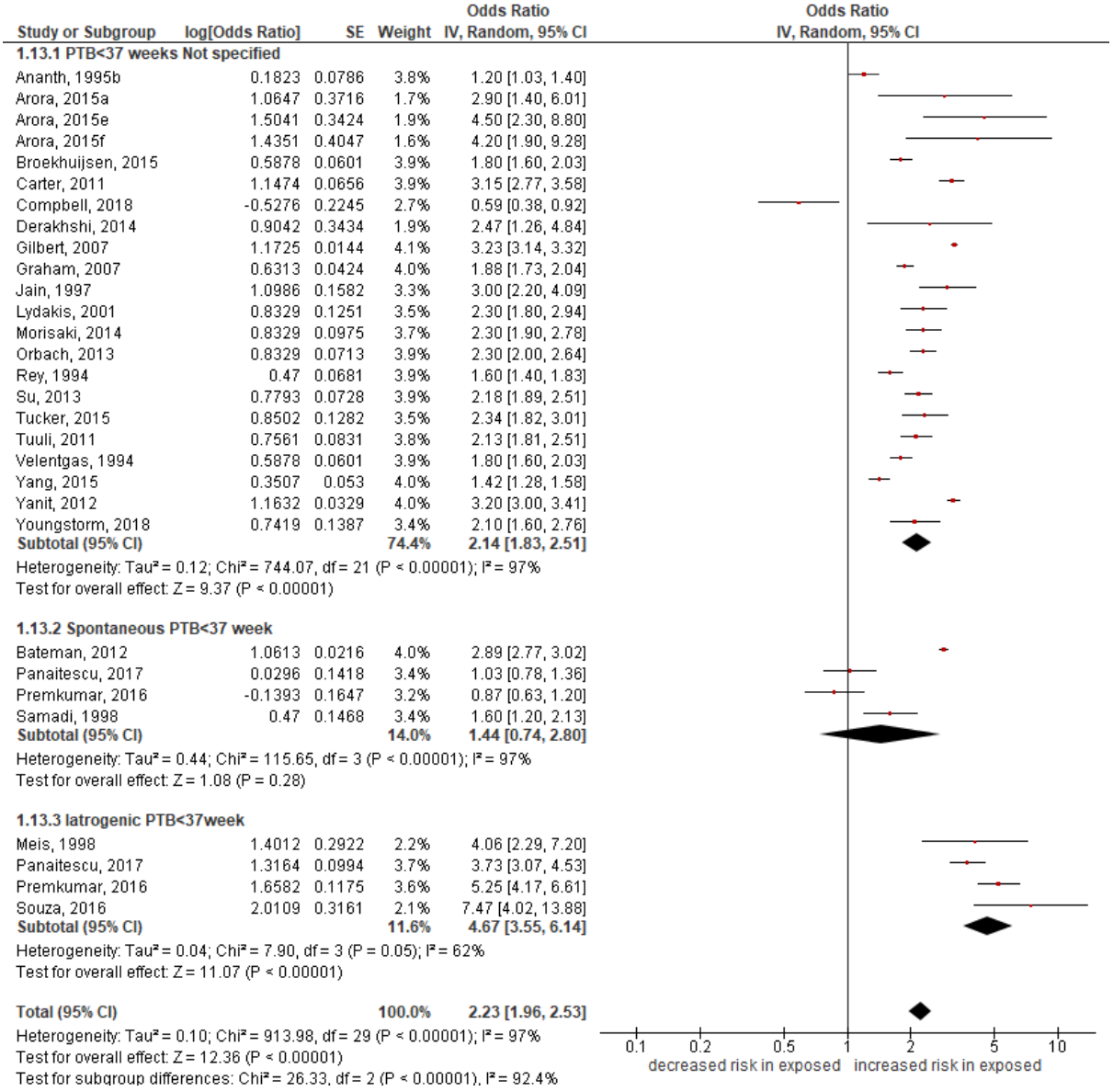


Figure S8c: Funnel plot for adjusted estimates of PTB (chronic hypertension versus normotensive)

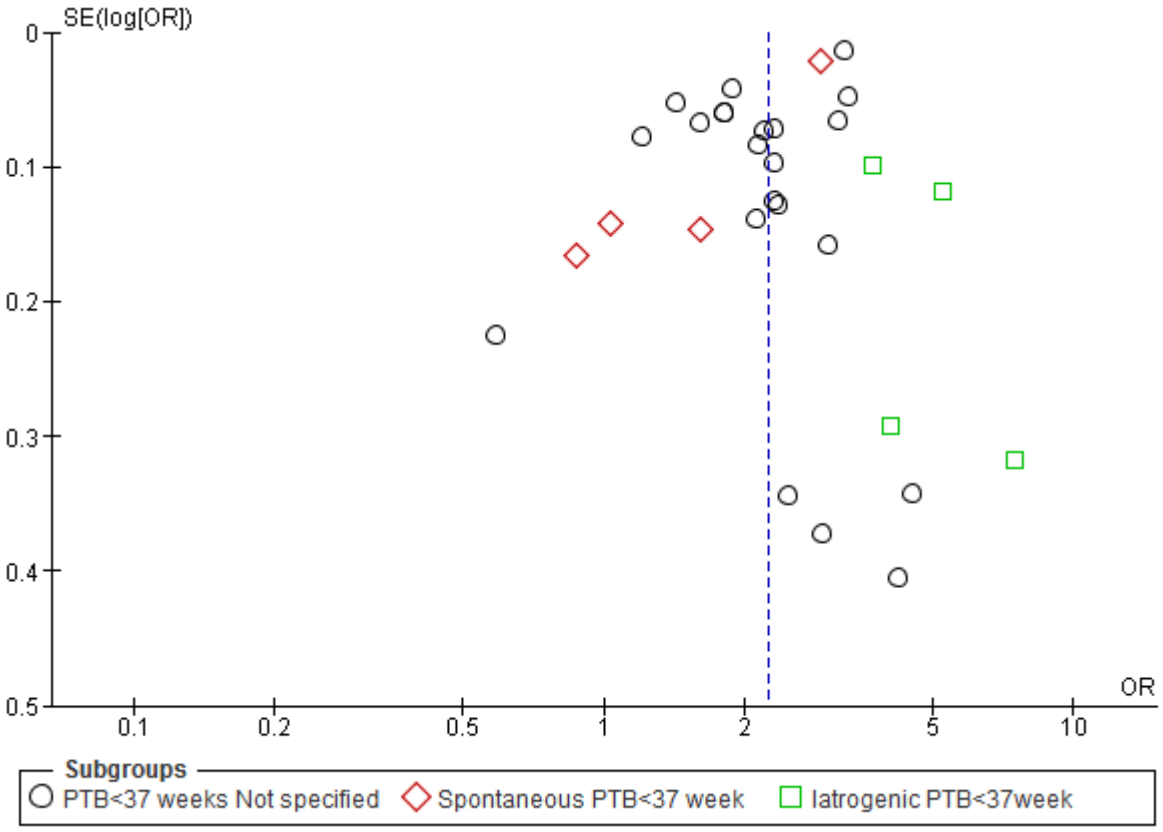


Figure S9a: Forest plot of crude estimates of the association between chronic hypertension and SGA

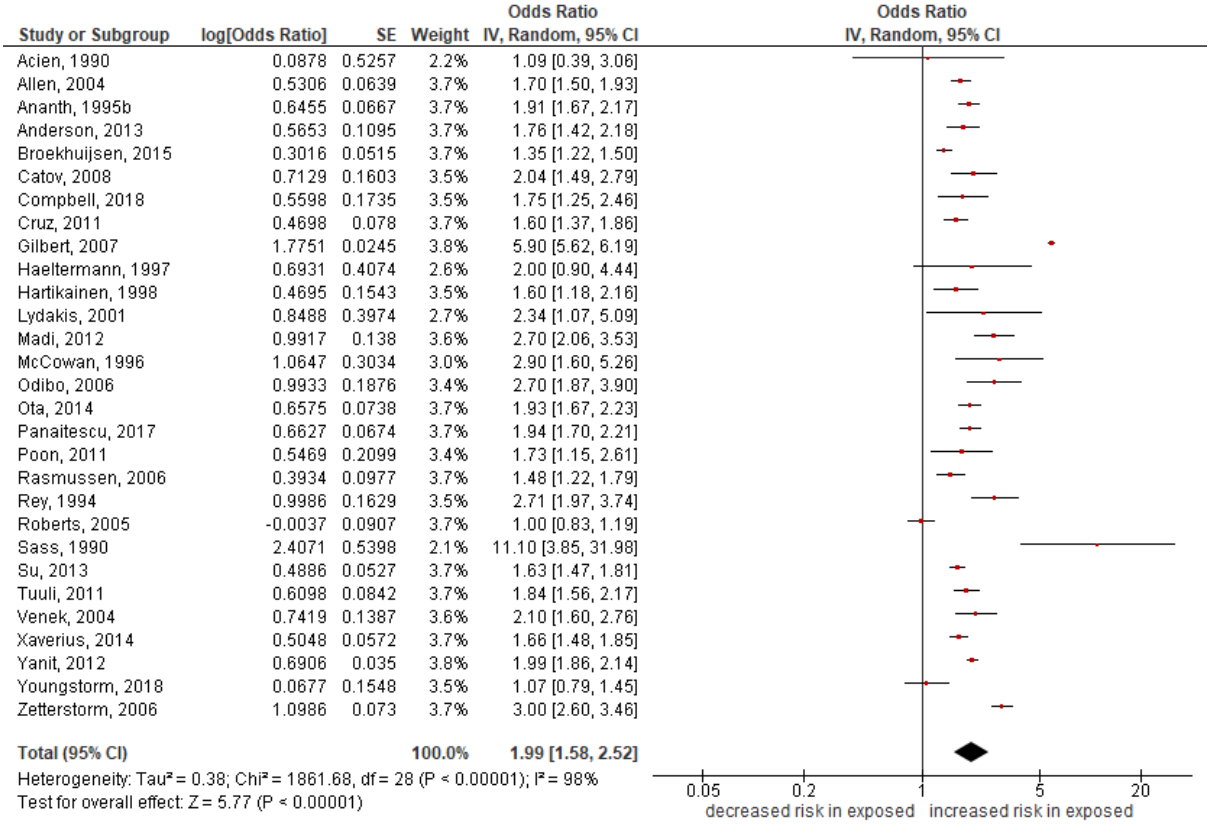


Figure S9b: Funnel plot for adjusted estimates of SGA (chronic hypertension versus normotensive)

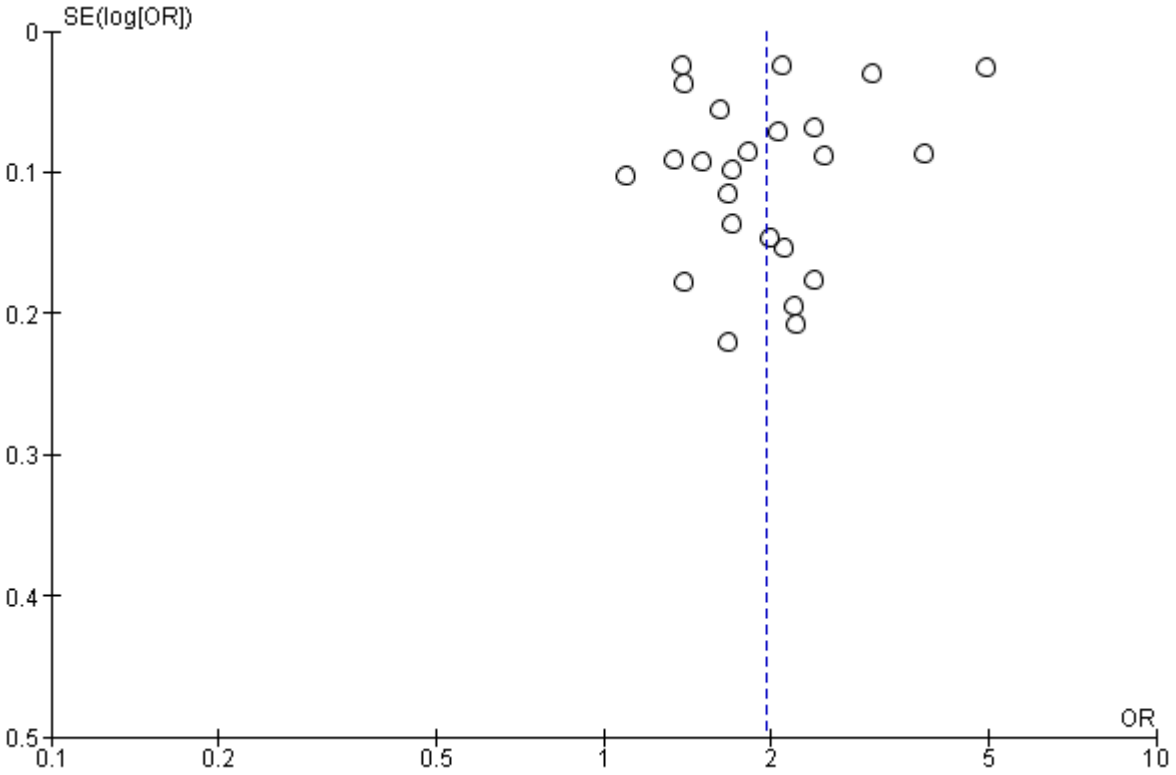


Figure S10a: Forest plot of crude estimates of the association between chronic hypertension and LBW

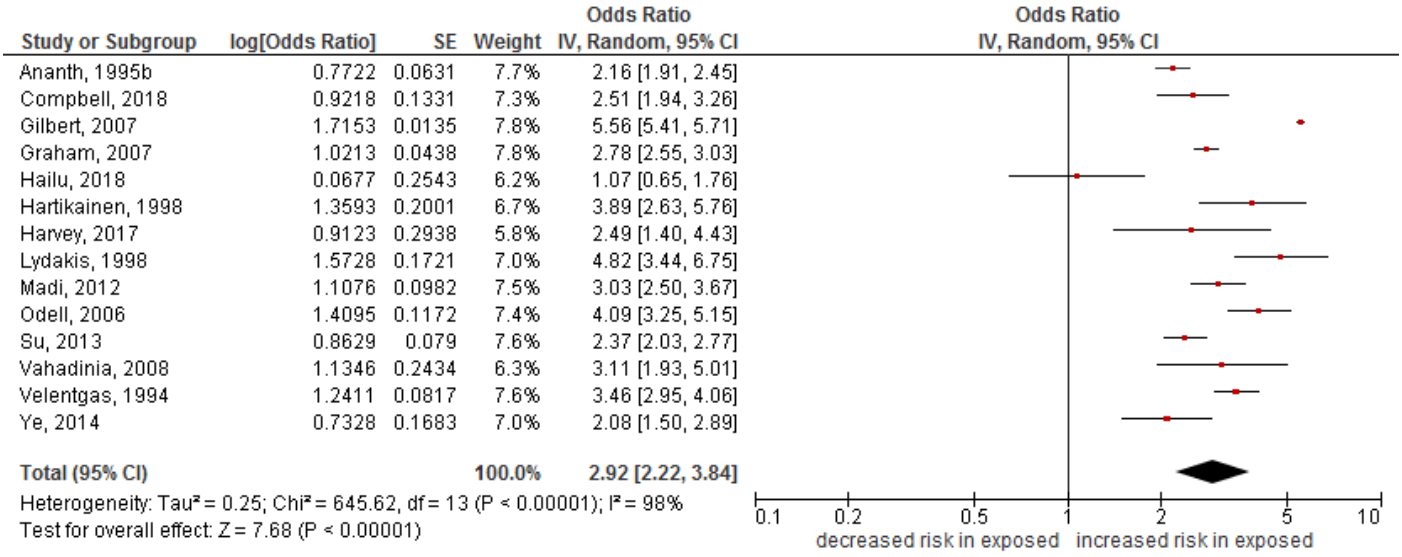


Figure S10b: Funnel plot for adjusted estimates of LBW (chronic hypertension versus normotensive)

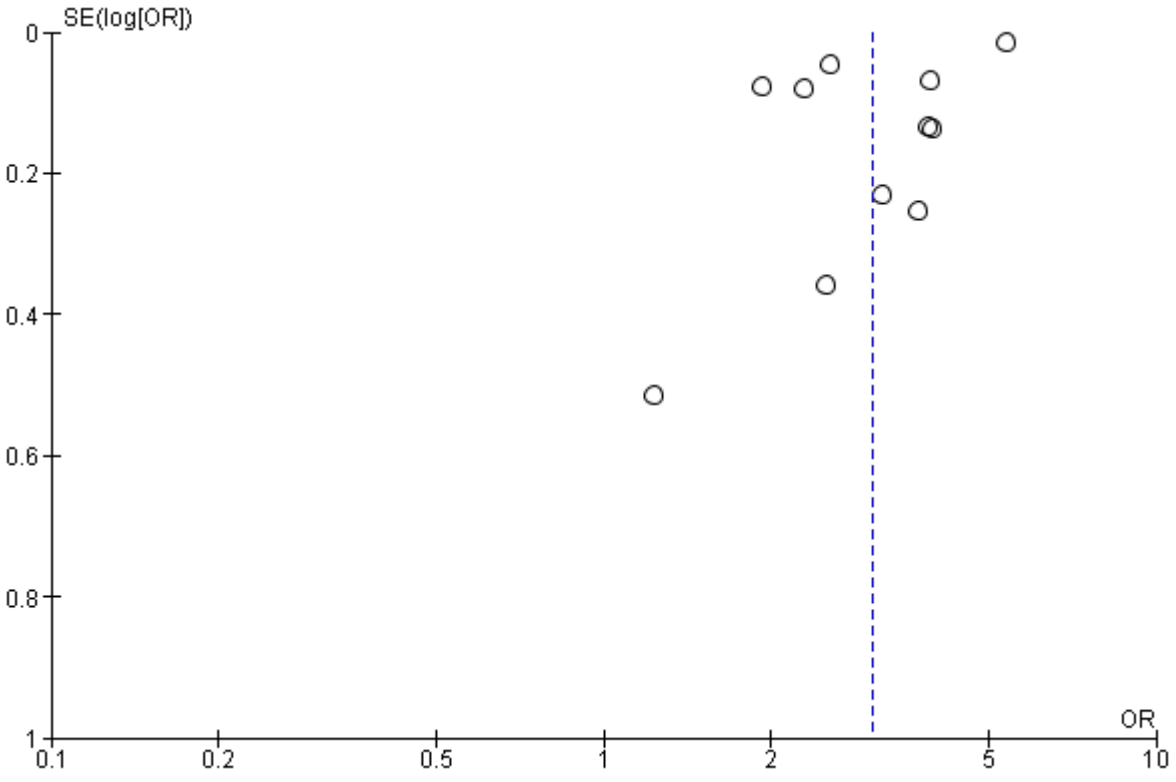


Figure S11a: Forest plot of crude estimates of the association between chronic hypertension and neonatal death

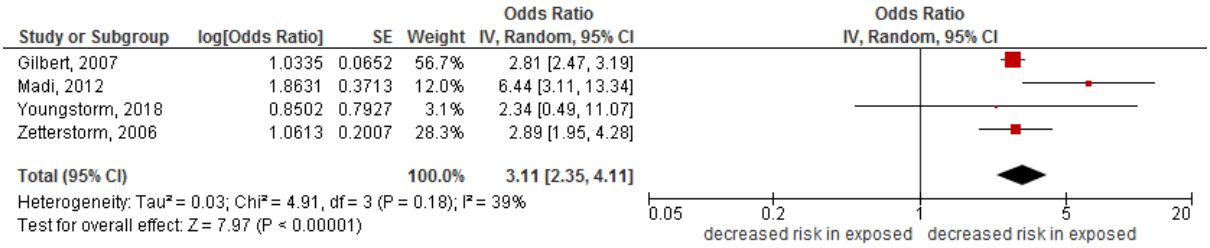


Figure S11b: Forest plot of adjusted estimates of the association between chronic hypertension and neonatal death

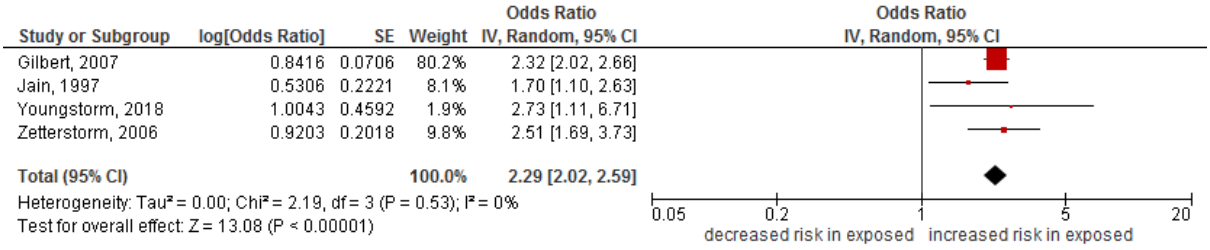


Figure S12a: Forest plot of crude estimates of the association between chronic hypertension and perinatal death

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Acien, 1990	1.8225	0.7323	4.7%	6.19 [1.47, 25.99]
Ahmed, 2012	0.8459	0.1317	14.9%	2.33 [1.80, 3.02]
Broekhuijsen, 2015	-0.3567	0.275	12.0%	0.70 [0.41, 1.20]
Hartikainen, 1998	1.3371	0.3334	10.7%	3.81 [1.98, 7.32]
McCowan, 1996	0.5306	0.7382	4.6%	1.70 [0.40, 7.22]
Rey, 1994	1.3229	0.2909	11.6%	3.75 [2.12, 6.64]
Sass, 1990	1.6045	0.5658	6.5%	4.98 [1.64, 15.08]
Venek, 2004	0.5306	0.2221	13.1%	1.70 [1.10, 2.63]
Ye, 2014	1.296	0.2499	12.5%	3.65 [2.24, 5.96]
Youngstorm, 2018	0.7839	0.4	9.3%	2.19 [1.00, 4.80]
Total (95% CI)			**100.0%**	**2.46 [1.70, 3.55]**

Heterogeneity: Tau² = 0.22; Chi² = 33.00, df = 9 (P = 0.0001); I² = 73%
Test for overall effect: Z = 4.79 (P < 0.00001)

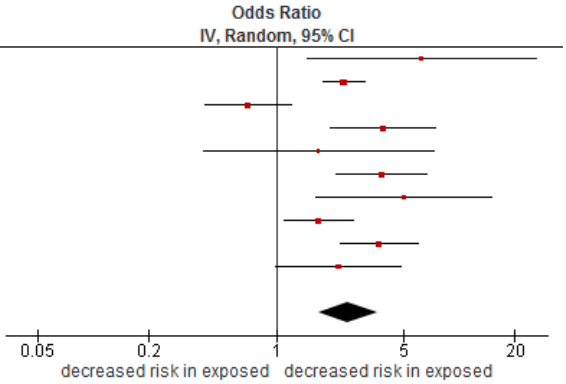


Figure S12b: Forest plot of adjusted estimates of the association between chronic hypertension and perinatal death

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Ahmed, 2012	0.802	0.1325	20.7%	2.23 [1.72, 2.89]
Broekhuijsen, 2015	-0.2231	0.2398	16.3%	0.80 [0.50, 1.28]
Jain, 1997	0.8755	0.1468	20.2%	2.40 [1.80, 3.20]
Rey, 1994	1.1632	0.2936	14.1%	3.20 [1.80, 5.69]
Venek, 2004	0.47	0.2398	16.3%	1.60 [1.00, 2.56]
Youngstorm, 2018	0.6366	0.3403	12.4%	1.89 [0.97, 3.68]
Total (95% CI)			**100.0%**	**1.87 [1.33, 2.63]**

Heterogeneity: Tau² = 0.13; Chi² = 20.27, df = 5 (P = 0.001); I² = 75%
Test for overall effect: Z = 3.60 (P = 0.0003)

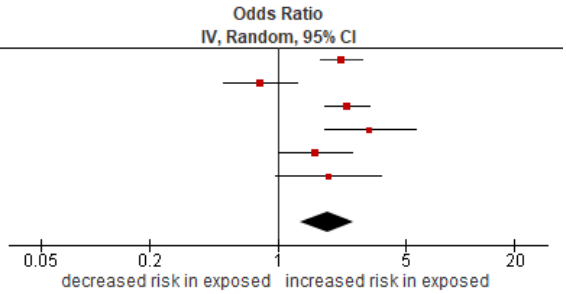


Figure S13: Forest plot of crude estimates of the association between chronic hypertension and NICU admission

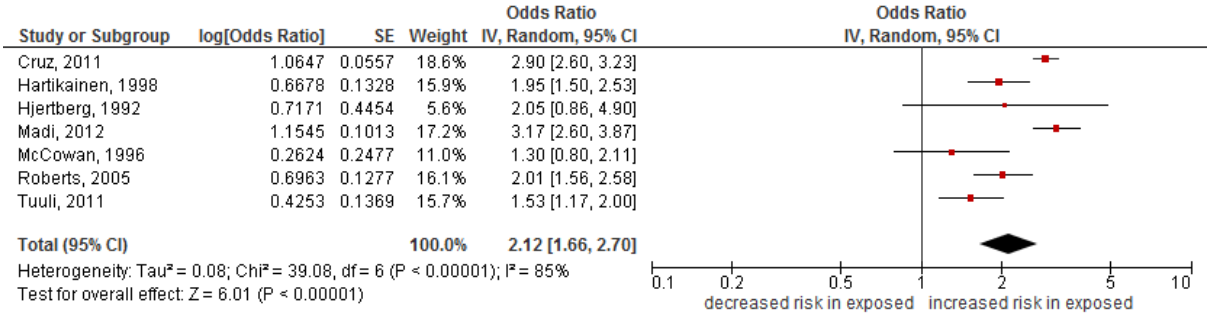


Figure S14: Forest plot of crude estimates of the association between chronic hypertension and miscarriage

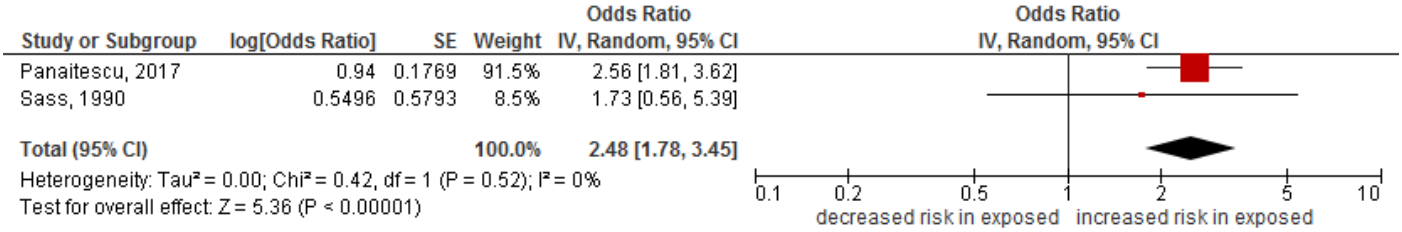


Figure S15: Forest plot of adjusted estimates of the association between chronic hypertension and stillbirth by ethnicity

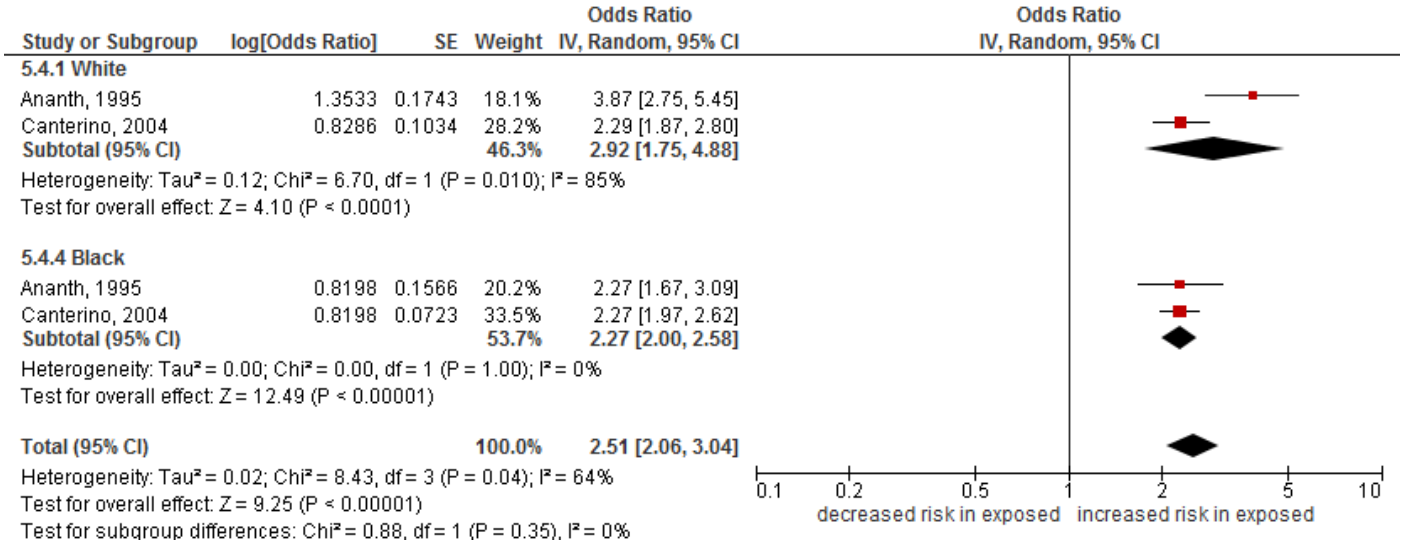


Figure S16: Forest plot of adjusted estimates of the association between chronic hypertension and PTB by ethnicity

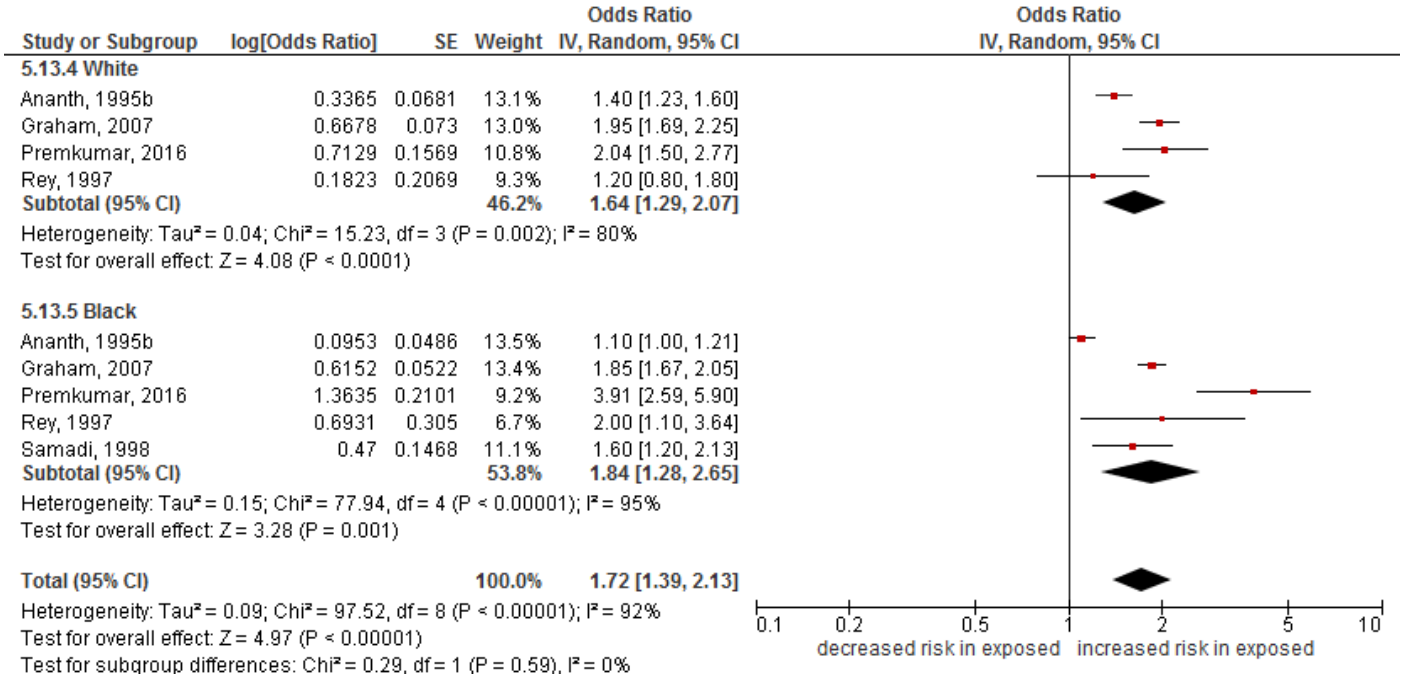


Figure S17: Forest plot of adjusted estimates of the association between chronic hypertension and SGA by ethnicity

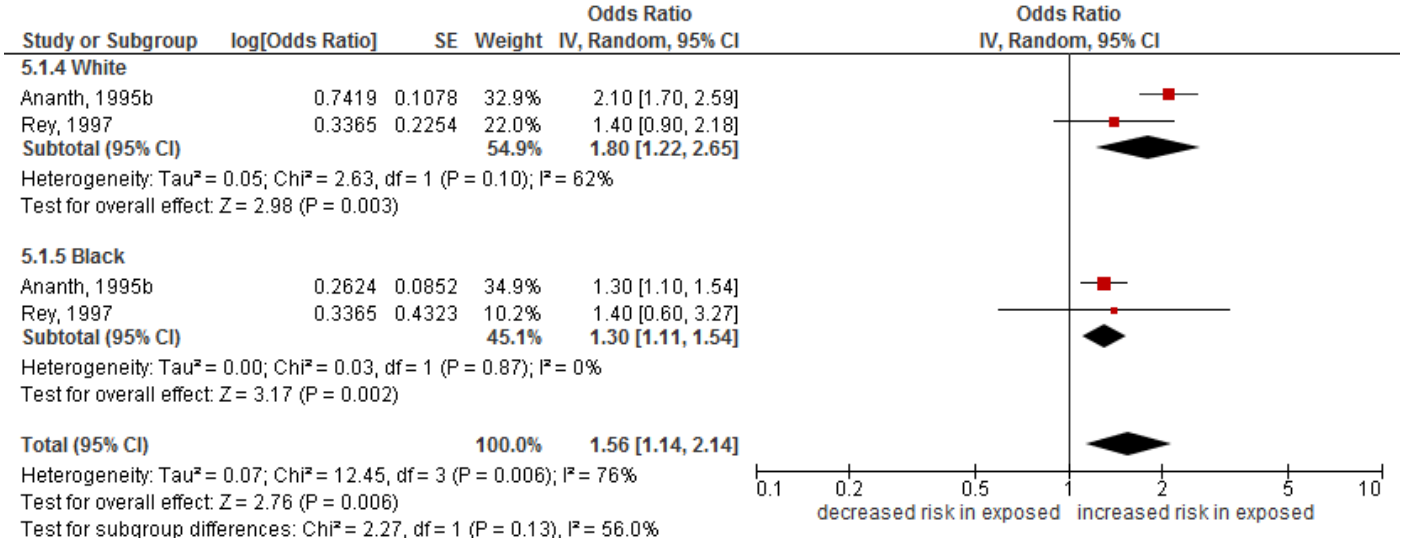
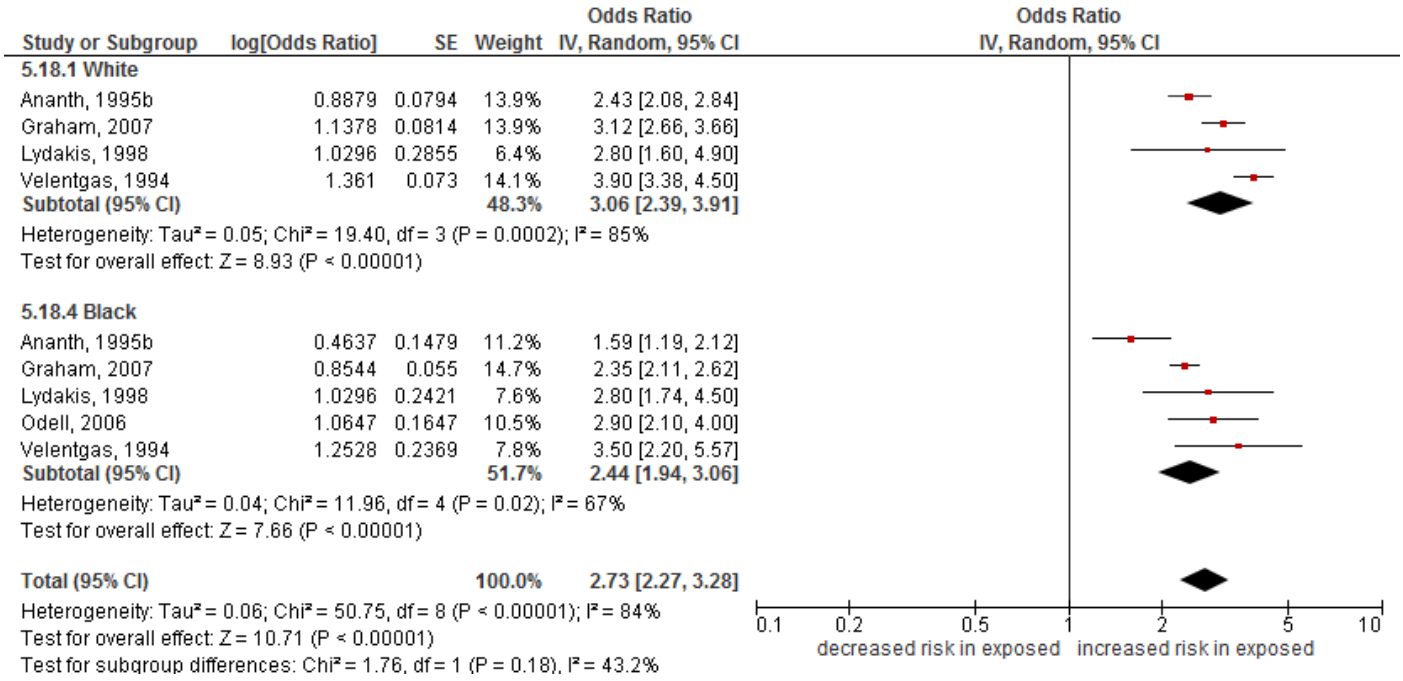


Figure S18: Forest plot of adjusted estimates of the association between chronic hypertension and LBW by ethnicity



Results of sensitivity analyses of adjusted estimates for adverse outcome by study location and year of publication (women with chronic hypertension vs. without)

Maternal Outcome	No. of studies (estimates)	Overall adjusted OR [95% CI]	I^2,%
PE			
Location			
North America	5	5.22 [2.87, 9.50]	100
Europe	4	4.83 [3.14, 7.42]	97
Other	8	6.01 [3.34, 10.79]	99
Decades			
1990-1999	1	6.50 [5.20, 8.13]	-
2000-2009	7	3.25 [1.74, 6.07]	99
2010-2019	14	7.29 [6.15, 8.65]	97
HELLP			
Location			
North America	1	2.66 [2.14, 3.31]	-
Europe	2	3.15 [1.09, 9.15]	80
Decades			
2000-2009	1	2.66 [2.14, 3.31]	-
2010-2019	2	3.15 [1.09, 9.15]	80
CS			
Location			
North America	5	2.08 [1.88, 2.31]	95
Europe	2	1.11 [1.01, 1.21]	0
Other	1	2.70 [2.40, 3.04]	-
Decades			
1990-1999	1	1.80 [1.60, 2.03]	-
2000-2009	2	2.48 [2.15, 2.86]	83
2010-2019	5	1.71 [1.28, 2.30]	98
PPH			
Location			
North America	2	1.45 [1.36, 1.54]	0
Europe	1	1.10 [0.90, 1.34]	-
Other	1	2.20 [1.40, 3.46]	-
Decades			

2000-2009	2	1.67 [1.12, 2.49]	70
2010-2019	2	1.32 [0.87, 2.02]	74
Maternal mortality			
Location			
North America	4	4.80 [3.04, 7.58]	71
Decades			
2000-2009	2	3.66 [2.00, 6.69]	55
2010-2019	2	6.04 [3.82, 9.53]	46
Fetal, neonatal outcome			
Stillbirth			
Location			
North America	12	2.37 [2.25, 2.50]	3
Europe	4	2.18 [1.87, 2.55]	0
Other	2	2.27 [2.03, 2.54]	0
Decades			
1990-1999	2	2.89 [2.39, 3.49]	0
2000-2009	7	2.34 [2.21, 2.47]	0
2010-2019	9	2.26 [2.10, 2.44]	0
VPTB<34 wks.			
Location			
North America	3	2.51 [0.91, 6.92]	99
Europe	2	1.55 [1.15, 2.09]	0
Other	1	1.25 [1.02, 1.53]	-
Decades			
1990-1999	1	1.40 [1.20, 1.63]	-
2000-2009	-	-	-
2010-2019	5	2.06 [1.06, 3.98]	97
PTB<37 wks.*			
Location			
North America	16	2.08 [1.76, 2.46]	96
Europe	5	2.56 [1.90, 3.44]	78
Other	5	2.04 [1.58, 2.63]	91
Decades			

1990-1999	5	1.93 [1.40, 2.66]	90
2000-2009	3	1.90 [1.73, 2.08]	36
2010-2019	18	2.26 [1.95, 2.61]	94
SGA			
Location			
North America	13	2.18 [1.62, 2.92]	99
Europe	6	1.81 [1.45, 2.27]	92
Australia	1	1.68 [1.34, 2.11]	-
Other	4	1.62 [1.39, 1.89]	58
Decades			
1990-1999	3	2.50 [1.44, 4.35]	95
2000-2009	7	2.30 [1.49, 3.56]	98
2010-2019	14	1.73 [1.44, 2.07]	97
LBW			
Location			
North America	7	3.21 [2.19, 4.68]	98
Europe	1	3.91 [2.99, 5.11]	-
Other	3	2.46 [1.60, 3.77]	59
Decades			
1990-1999	3	3.07 [1.85, 5.10]	97
2000-2009	4	3.74 [2.28, 6.14]	99
2010-2019	4	2.38 [1.95, 2.92]	13
Neonatal death			
Perinatal mortality			
Location			
North America	3	2.45 [1.92, 3.11]	0
Europe	2	1.36 [0.50, 3.72]	93
Other	1	1.60 [1.00, 2.56]	-
Decades			
1990-1999	2	2.54 [1.97, 3.29]	0
2000-2009	1	1.60 [1.00, 2.56]	-
2010-2019	3	1.51 [0.76, 2.99]	86

*Sub-group estimates (spontaneous, iatrogenic) for two studies were combined.

Figure S19a: Forest plot of crude estimates of the association between antihypertensive treatment and Pre-eclampsia

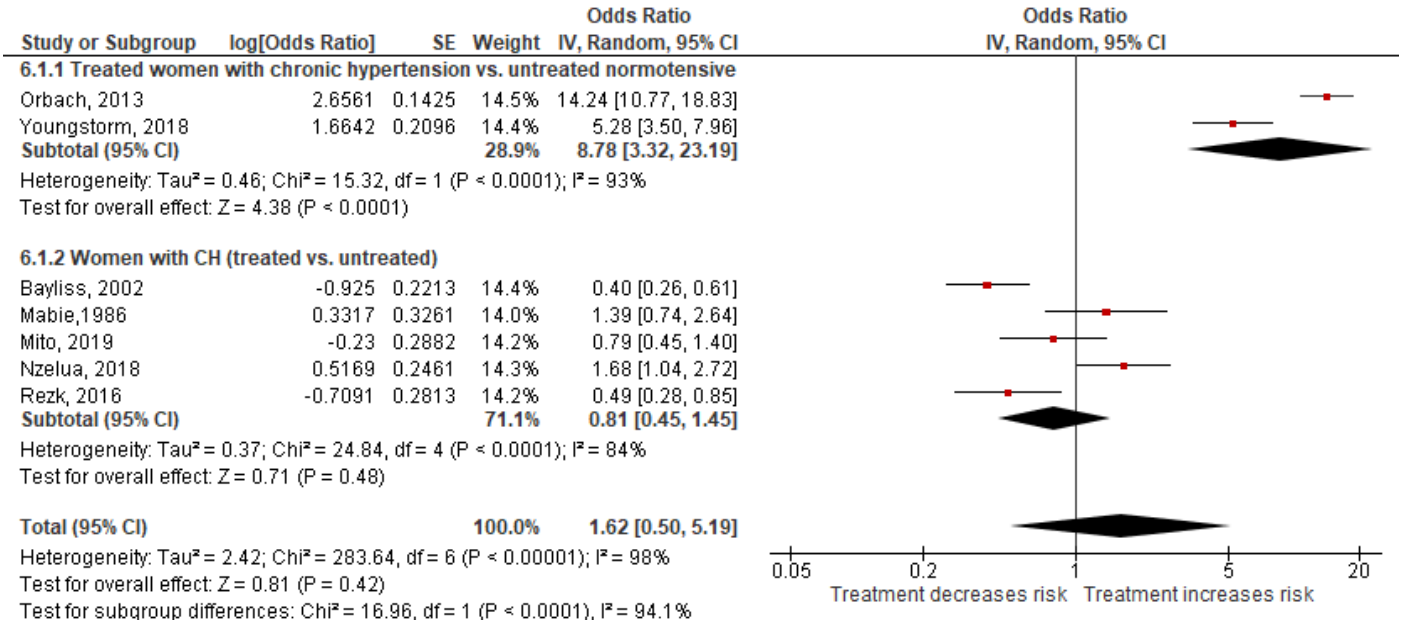


Figure S19b: Forest plot of adjusted estimates of the association between antihypertensive treatment and Pre-eclampsia

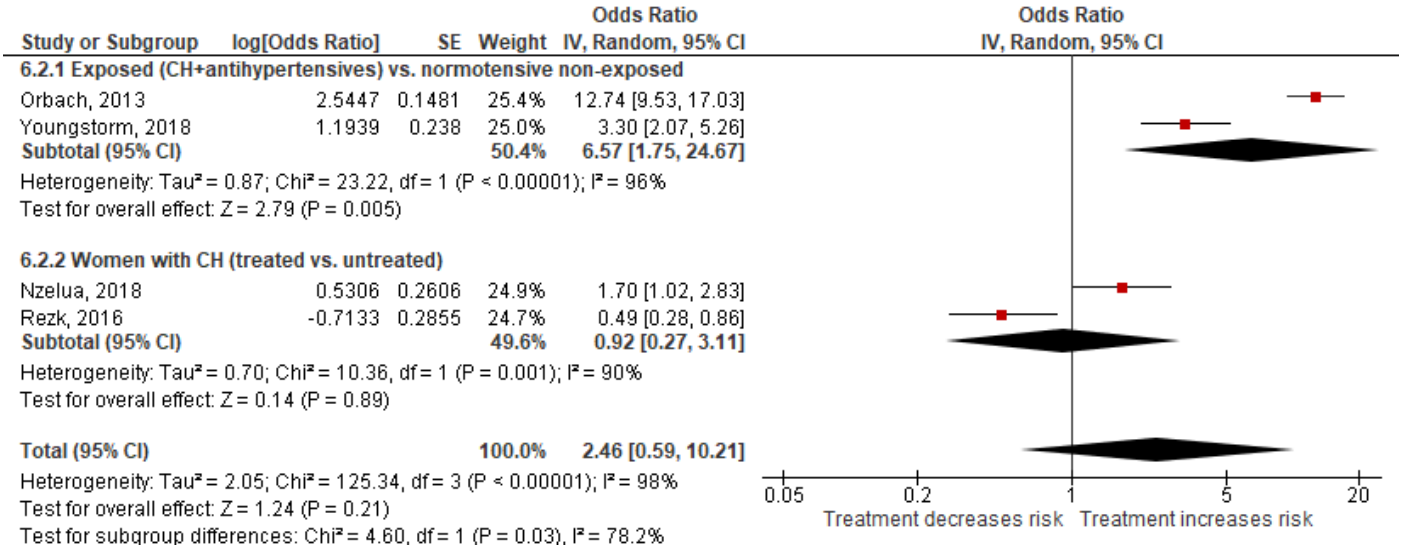


Figure S20: Forest plot of crude estimates of the association between antihypertensive treatment and caesarean section

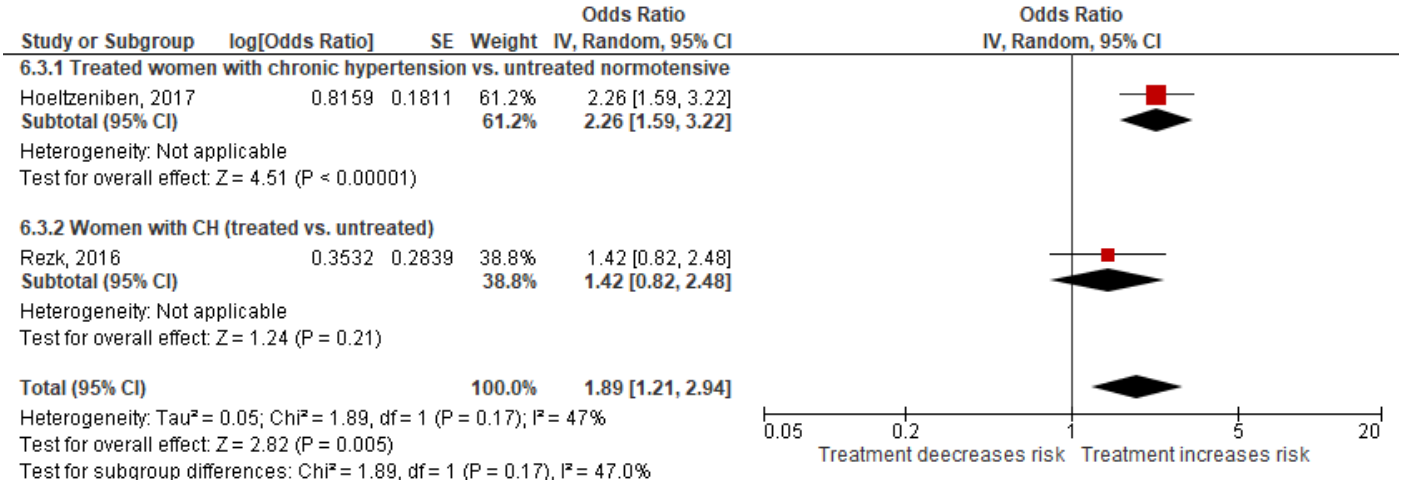


Figure S21: Forest plot of crude estimates of the association between antihypertensive treatment and miscarriage

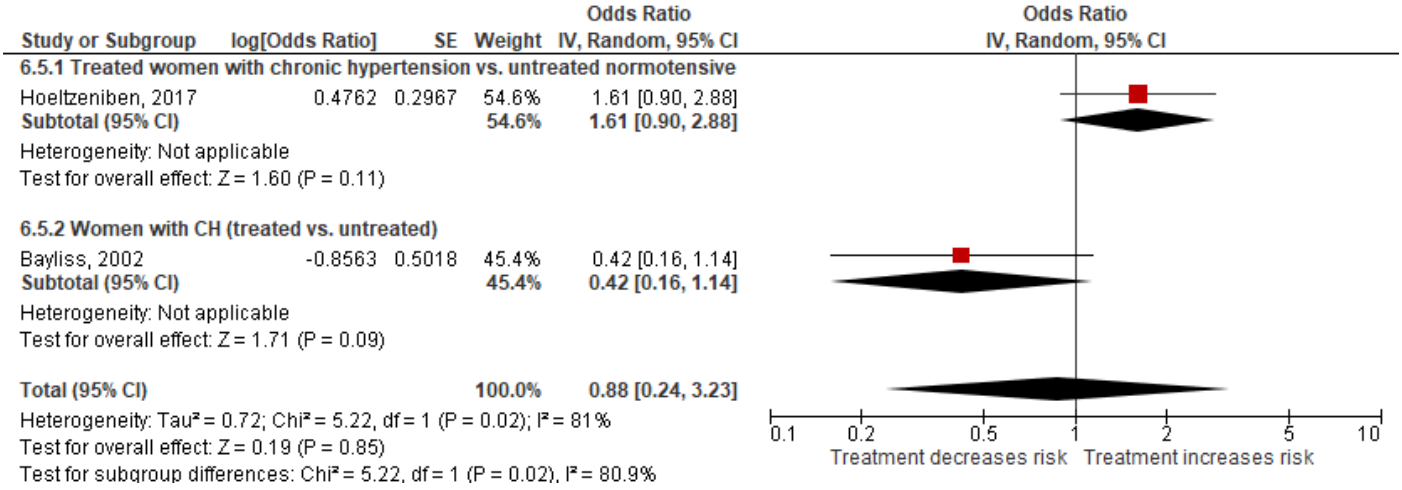


Figure S22: Forest plot of crude estimates of the association between antihypertensive treatment and stillbirth

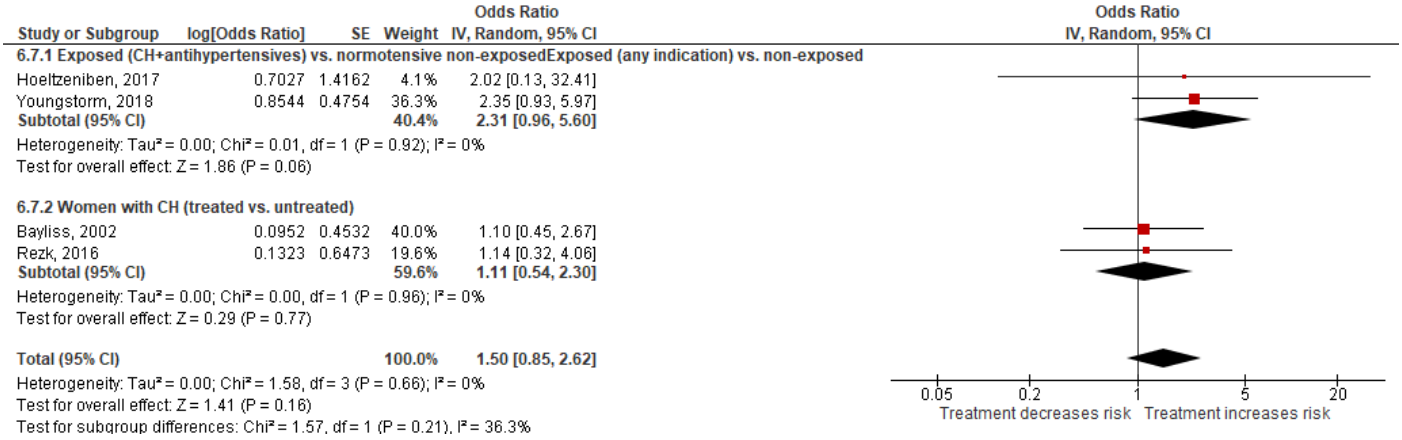


Figure S23a: Forest plot of crude estimates of the association between antihypertensive treatment and preterm birth

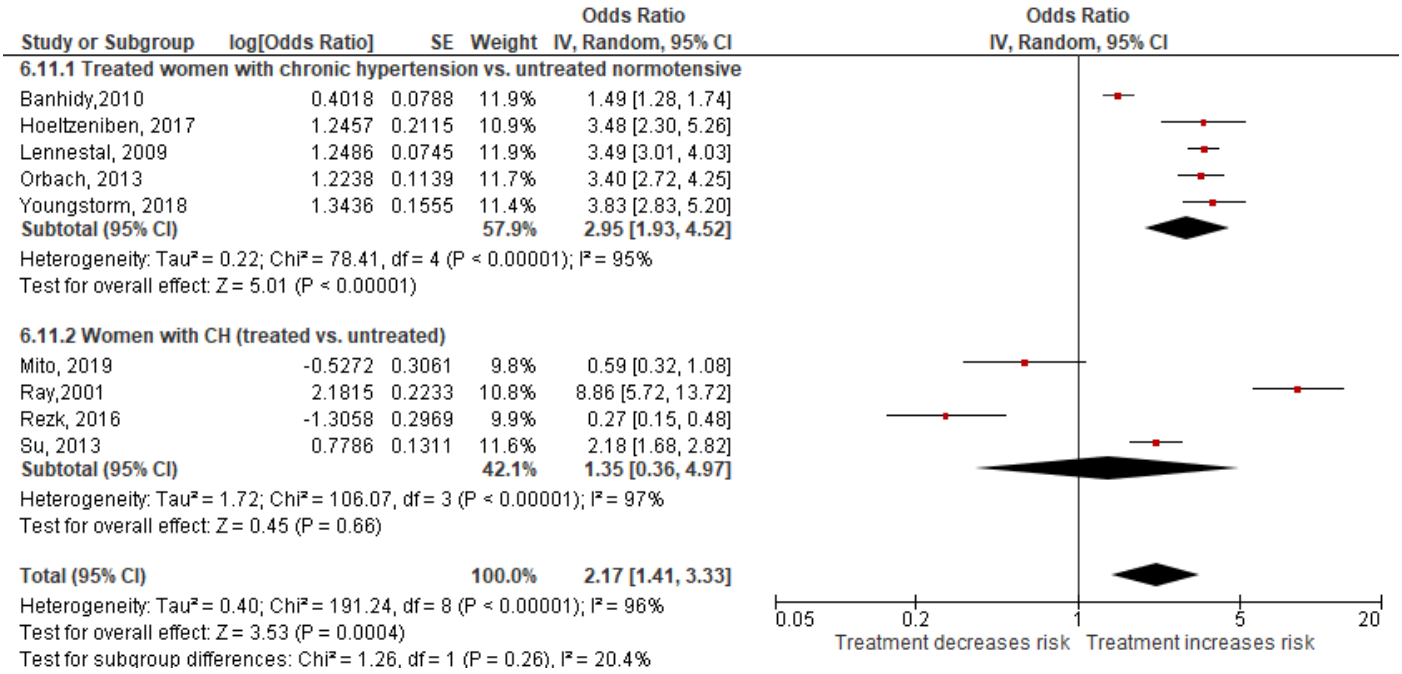


Figure S23b: Forest plot of adjusted estimates of the association between antihypertensive treatment and preterm birth

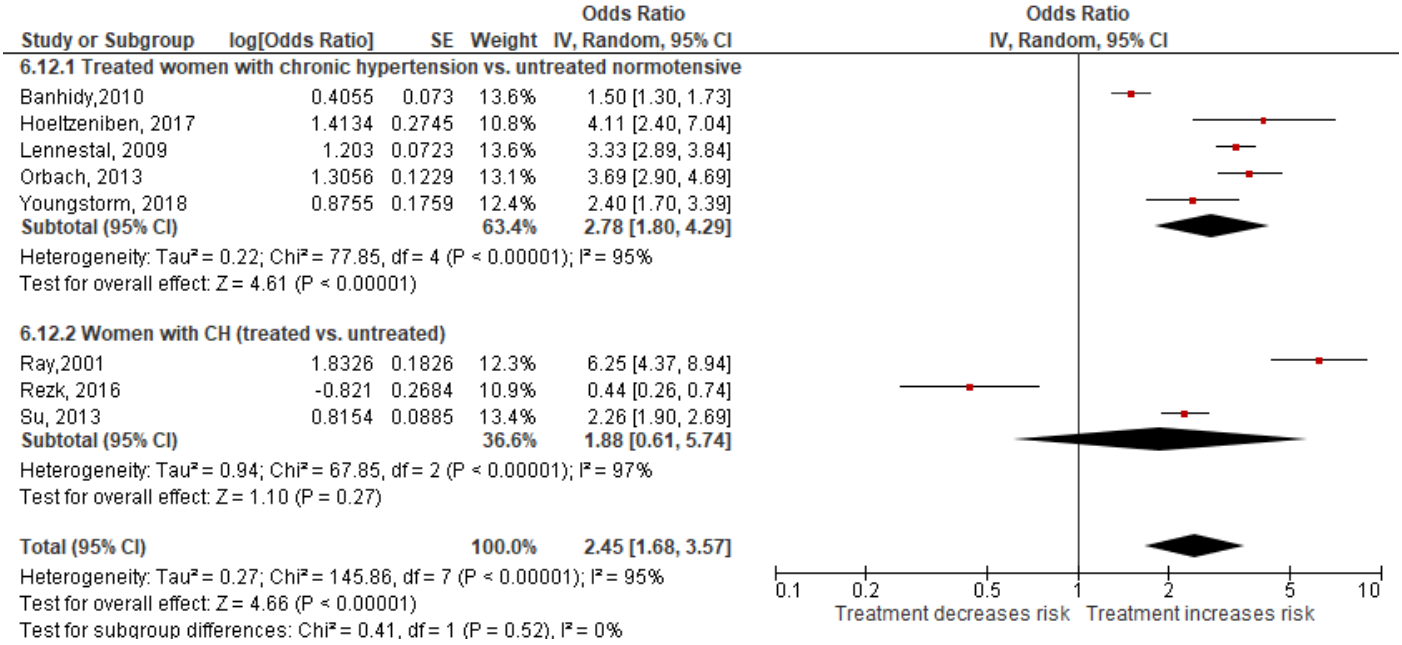


Figure S23c: Forest plot of crude estimates of the association between antihypertensive treatment and preterm birth (β-blockers vs. untreated)

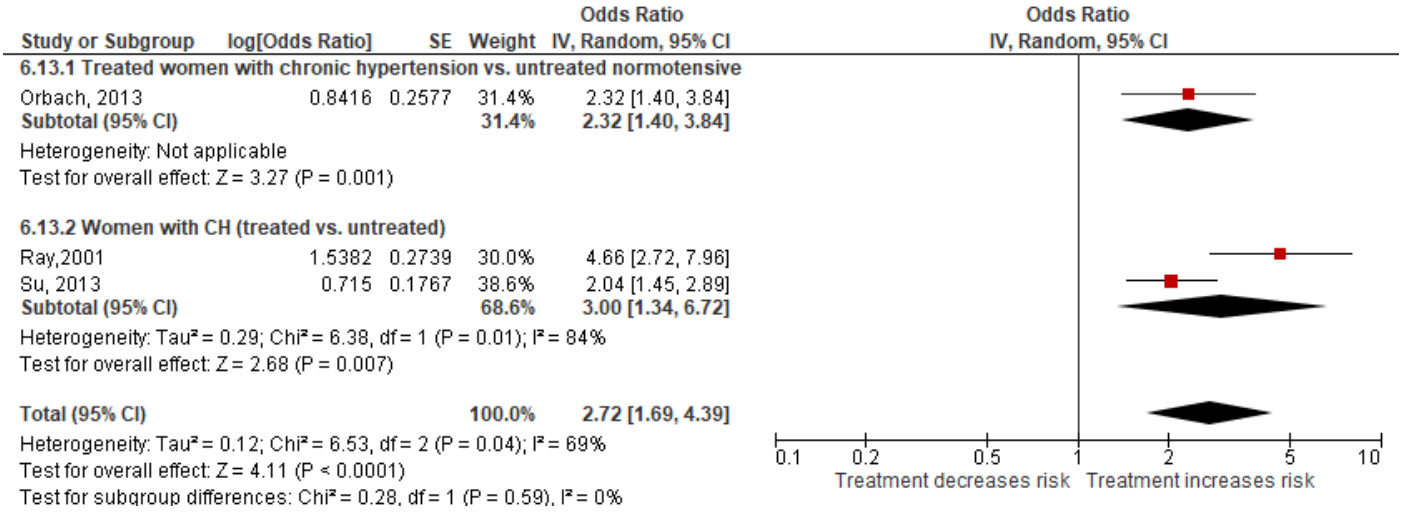


Figure S23d: Forest plot of adjusted estimates of the association between antihypertensive treatment and preterm birth (β-blockers vs. untreated)

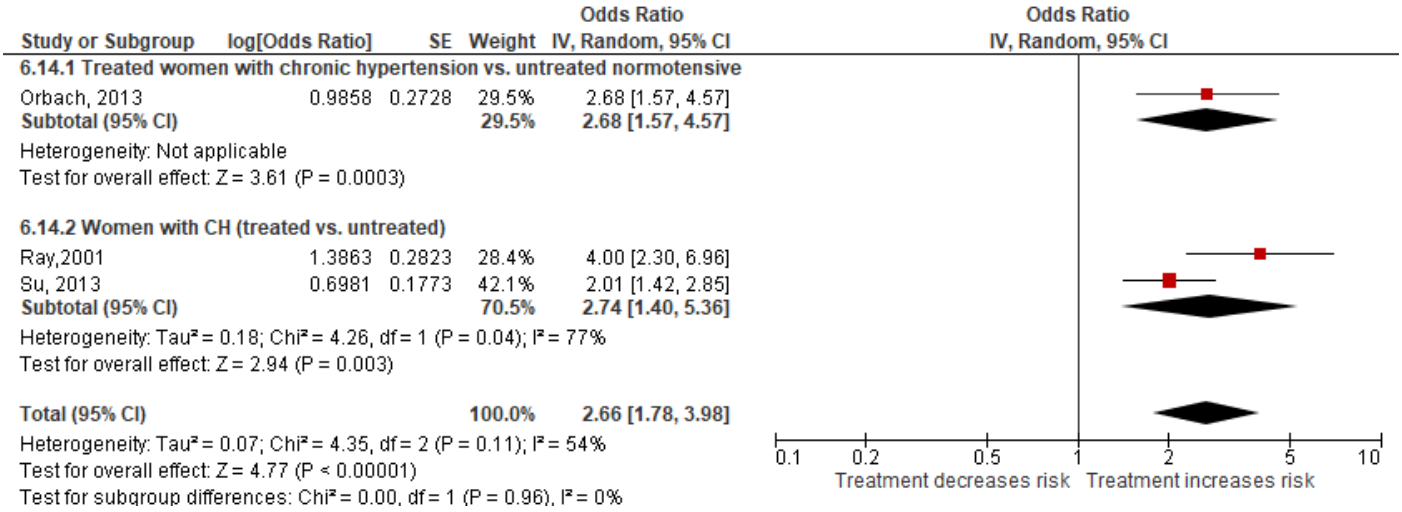


Figure S24a: Forest plot of crude estimates of the association between antihypertensive treatment and small for gestational age

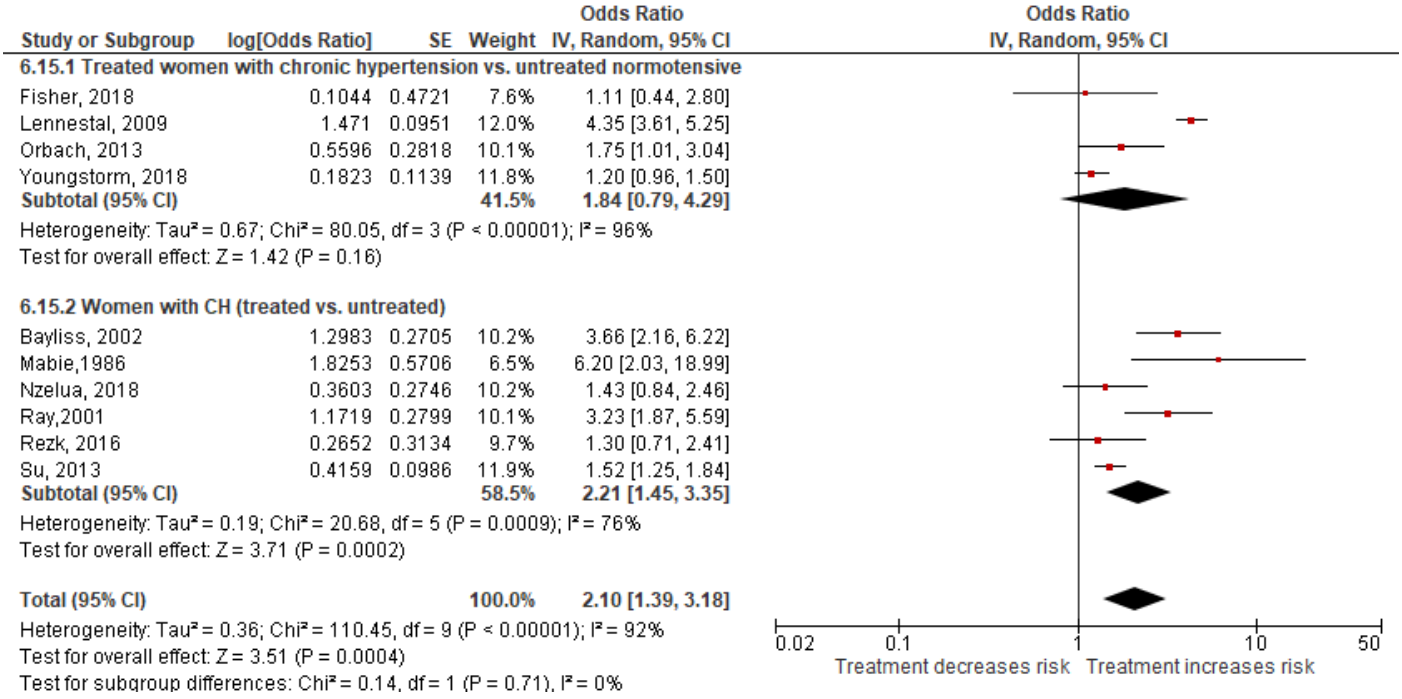


Figure S24b: Forest plot of adjusted estimates of the association between antihypertensive treatment and small for gestational age

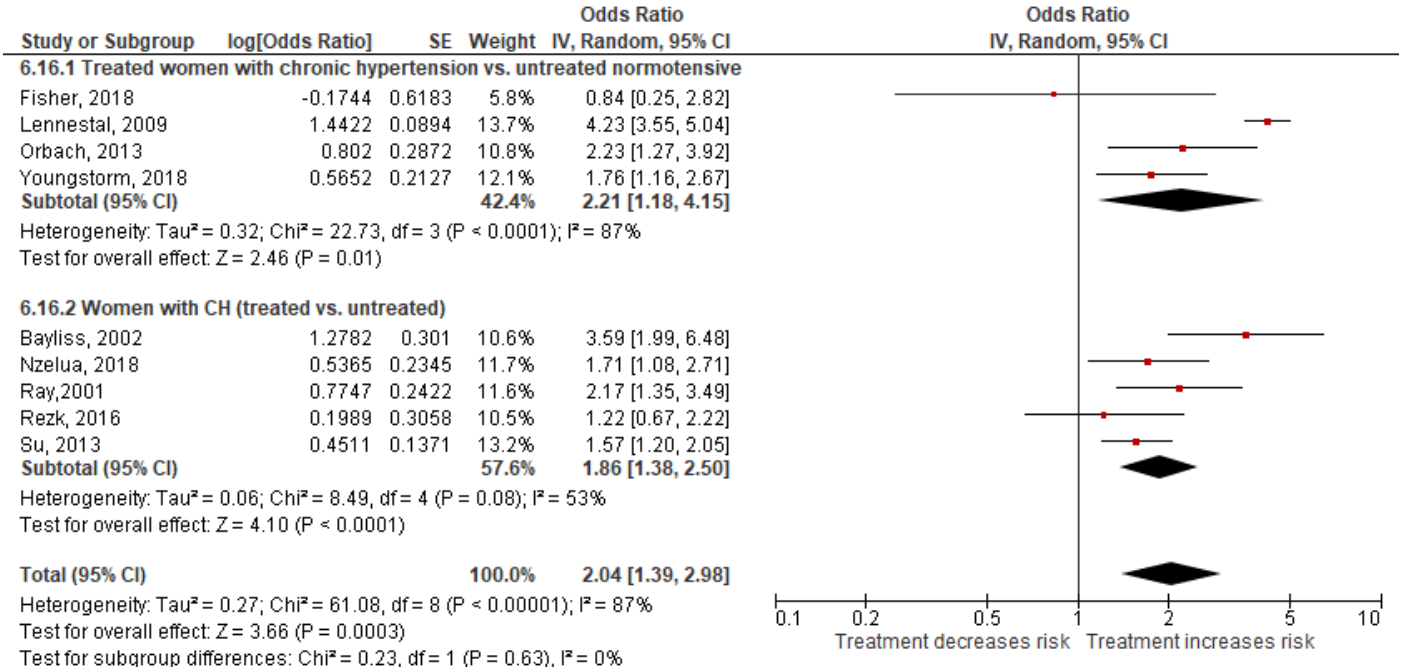


Figure S24c: Forest plot of crude estimates of small for gestational age (β-blockers only vs. untreated)

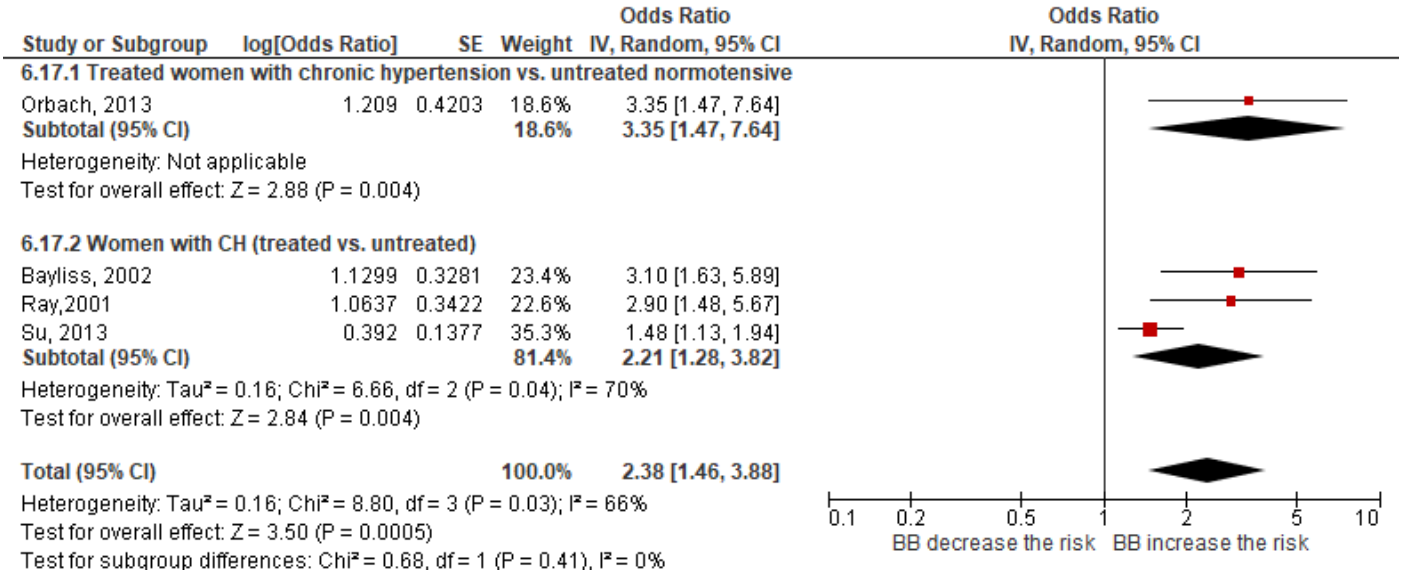


Figure S24d: Forest plot of adjusted of small for gestational age (β-blockers only vs. untreated)

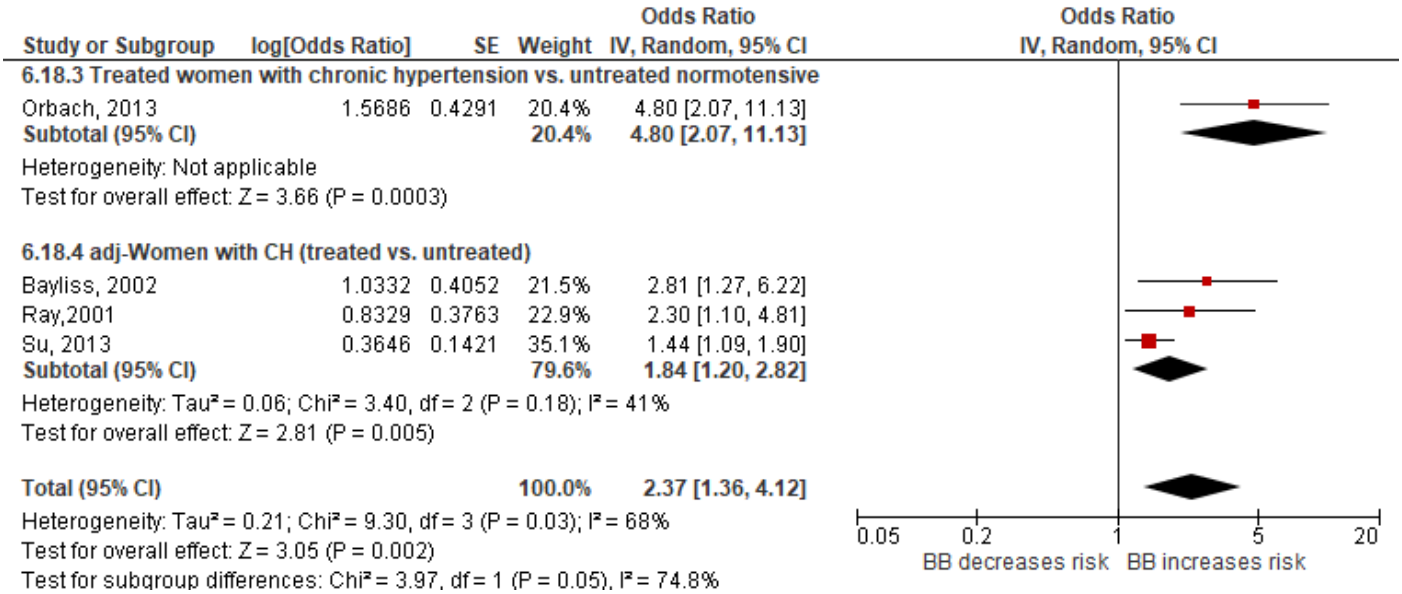


Figure S24e: Forest plot of crude estimates of small for gestational age (centrally acting antiadrenergic vs. untreated)

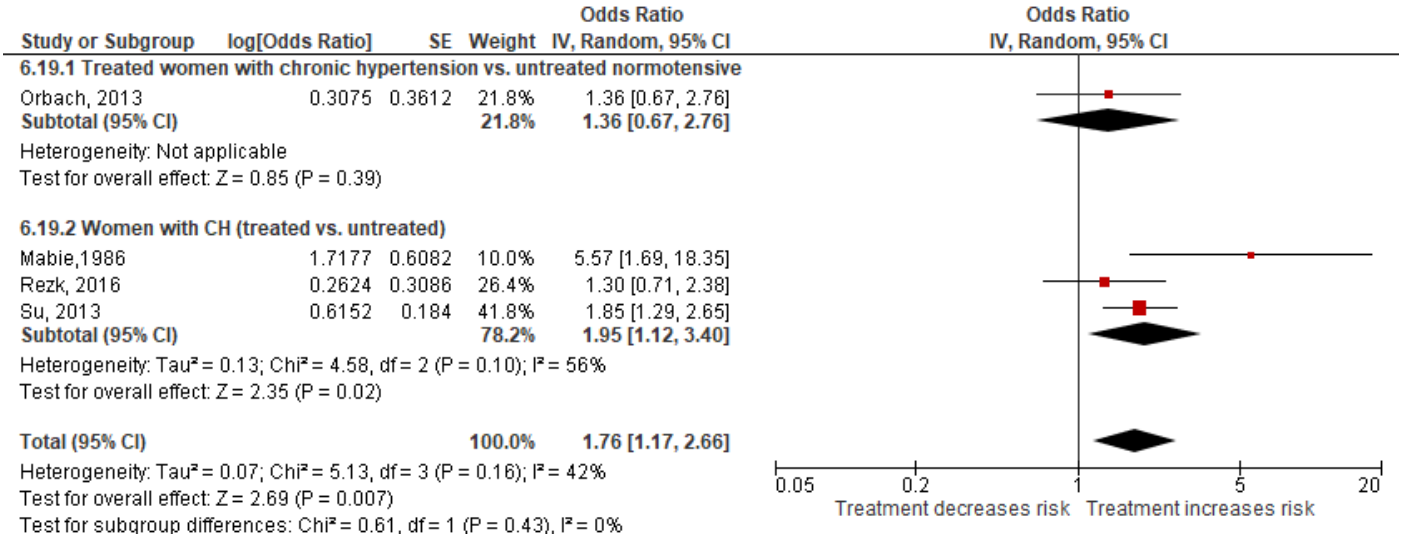


Figure S24f: Forest plot of adjusted estimates of small for gestational age (centrally acting antiadrenergic vs. untreated)

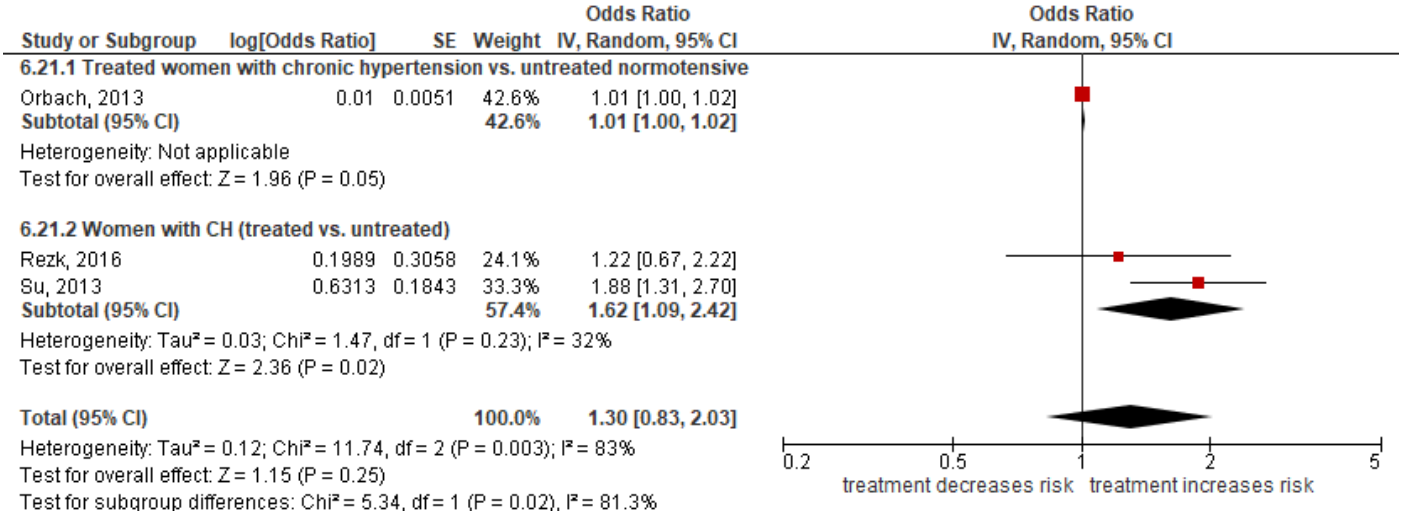


Figure S24g: Forest plot of adjusted estimates of small for gestational age (single/multiple agents vs. untreated)

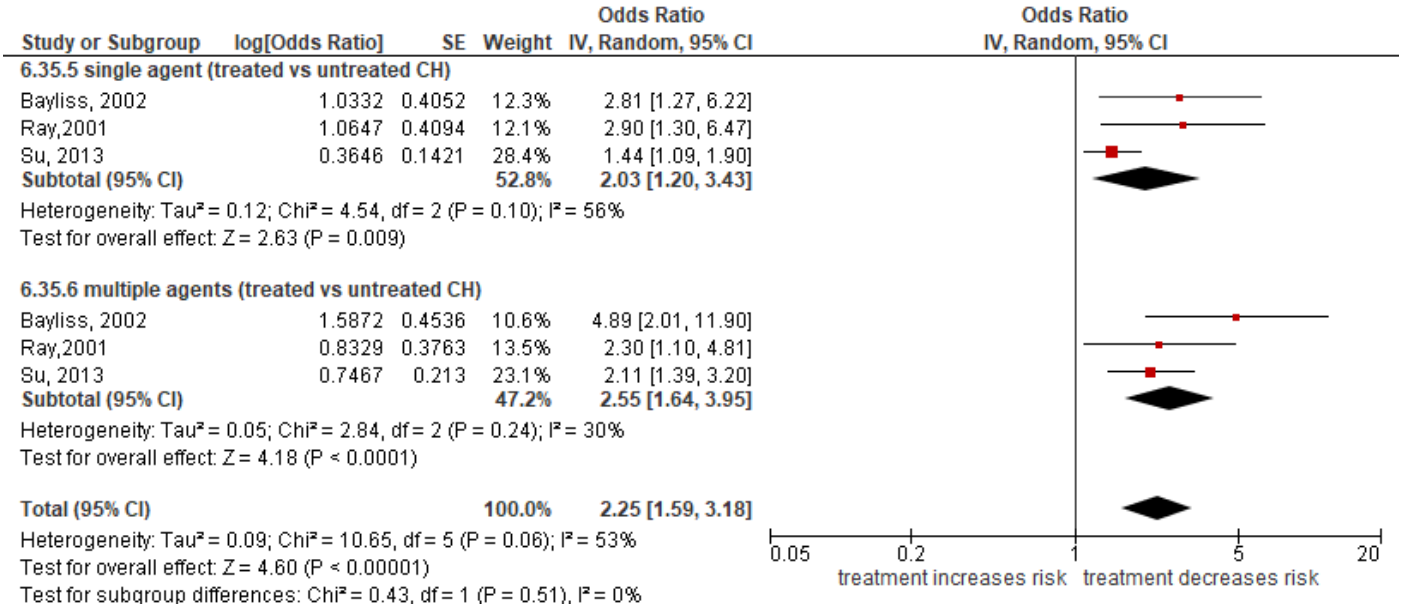


Figure S24h: Forest plot of crude estimates of small for gestational age (β-blockers vs. methyldopa)

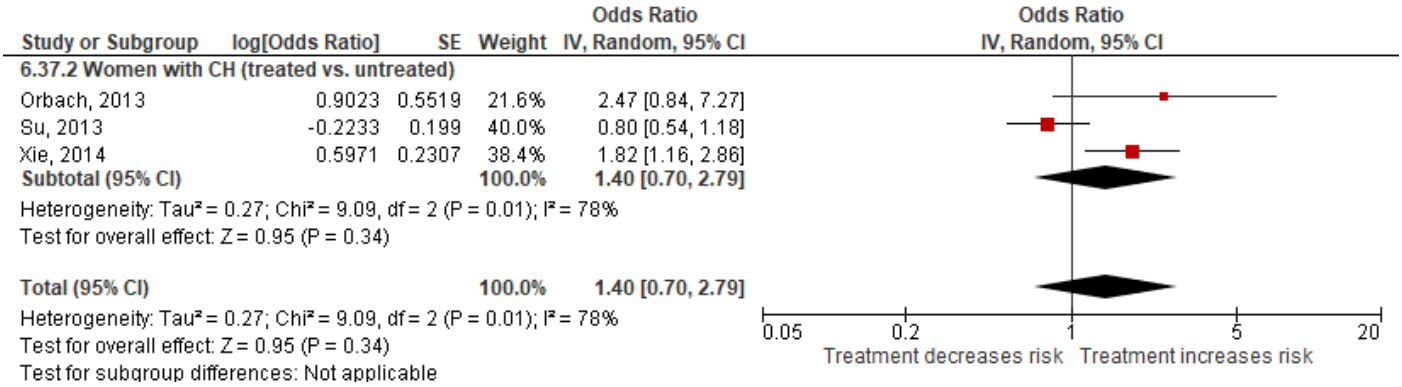


Figure S24i: Forest plot of crude estimates of SGA (methyldopa vs other agents)

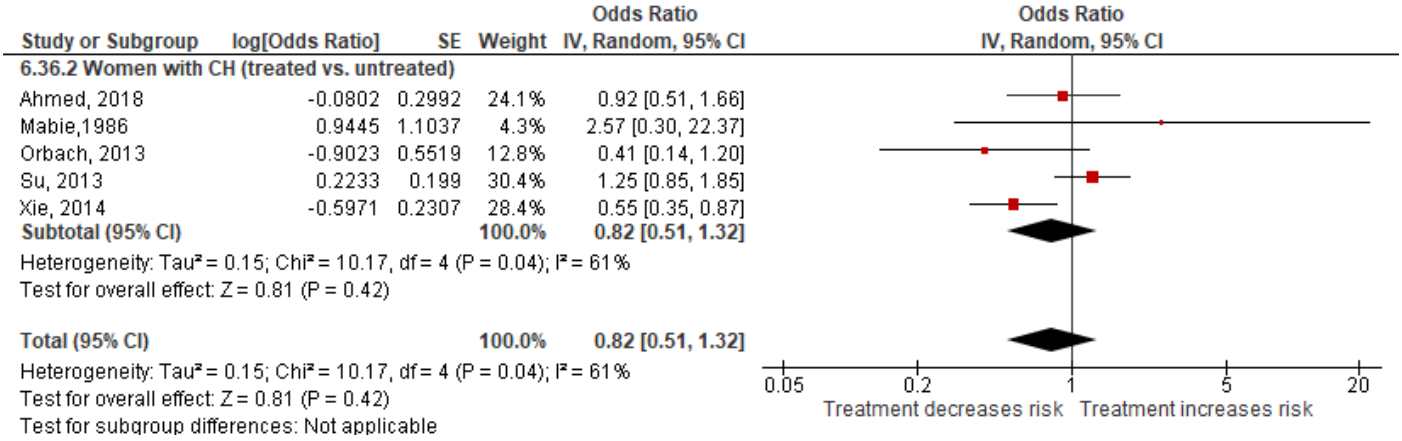


Figure S25a: Forest plot of crude estimates of the association between antihypertensive treatment and low birthweight

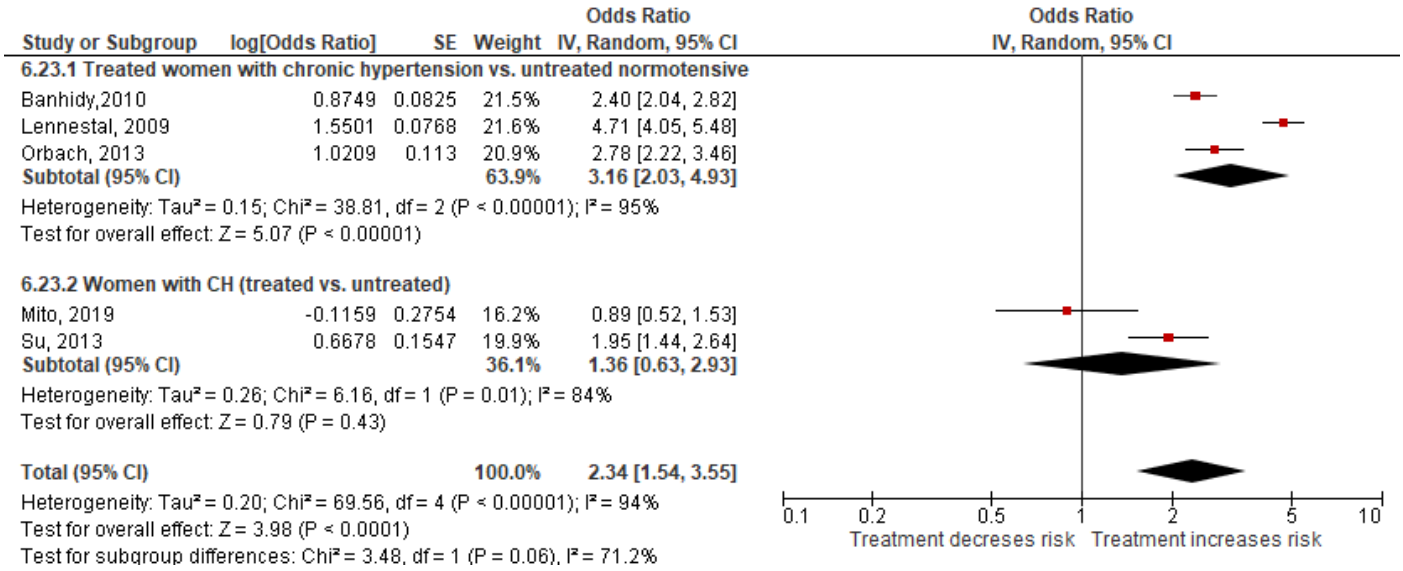


Figure S25b: Forest plot of adjusted estimates of the association between antihypertensive treatment and low birthweight

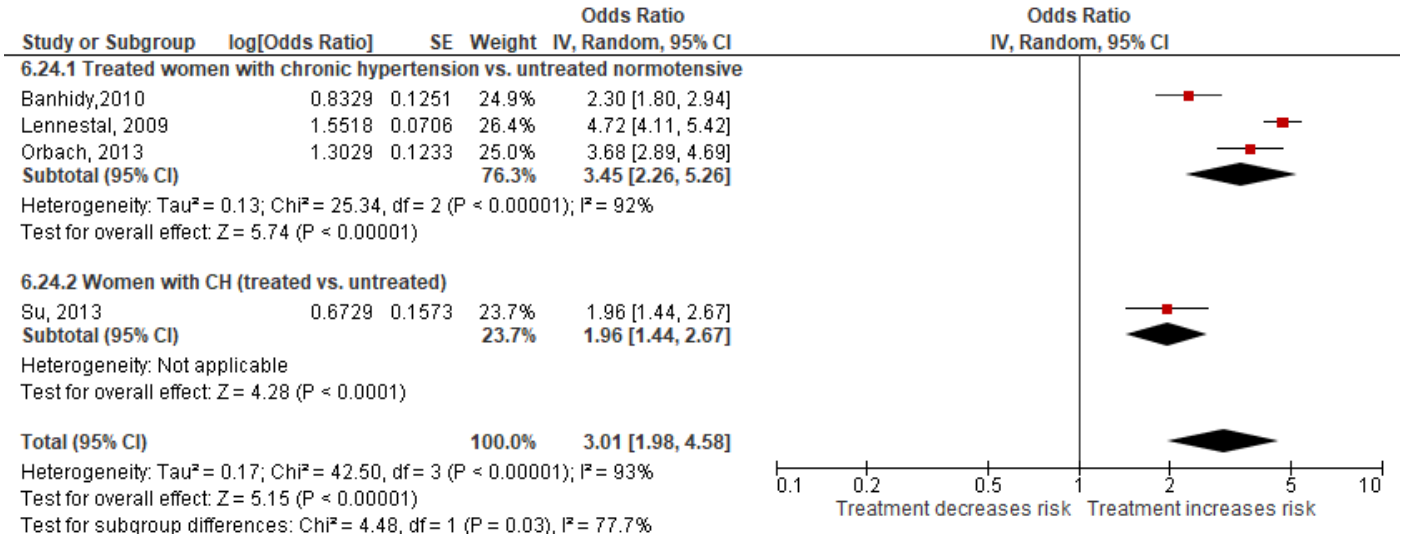


Figure S26: Forest plot of crude estimates of the association between antihypertensive treatment and neonatal intensive care unit admission