Future Cardiovascular Disease Risk for Women With Gestational Hypertension: A Systematic Review and Meta-Analysis

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BACKGROUND: Inconsistent findings have been found among studies evaluating the risk of cardiovascular disease for women who have had pregnancies complicated by gestational hypertension (the new onset of high blood pressure without proteinuria during pregnancy). We provide a comprehensive review of studies to quantify the association between gestational hypertension and cardiovascular events in women.

METHODS AND RESULTS: We conducted a systematic search of PubMed, Embase, and Web of Science in March 2019 for studies examining the association between gestational hypertension and any cardiovascular event. Two reviewers independently assessed the abstracts and full-text articles. Study characteristics and the relative risk (RR) of cardiovascular events associated with gestational hypertension were extracted from the eligible studies. Where appropriate, the estimates were pooled with inverse variance weighted random-effects meta-analysis. A total of 21 studies involving 360,1192 women (127,913 with gestational hypertension) were identified. Gestational hypertension in the first pregnancy was associated with a greater risk of overall cardiovascular disease (RR, 1.45; 95% CI, 1.17–1.80) and coronary heart disease (RR, 1.46; 95% CI, 1.23–1.73), but not stroke (RR, 1.26; 95% CI, 0.96–1.65) or thromboembolic events (RR, 0.88; 95% CI, 0.73–1.07). Women with 1 or more pregnancies affected by gestational hypertension were at greater risk of cardiovascular disease (RR, 1.81; 95% CI, 1.42–2.31), coronary heart disease (RR, 1.83; 95% CI, 1.33–2.51), and heart failure (RR, 1.77; 95% CI, 1.47–2.13), but not stroke (RR, 1.50; 95% CI, 0.75–2.99).

CONCLUSIONS: Gestational hypertension is associated with a greater risk of overall cardiovascular disease, coronary heart disease, and heart failure. More research is needed to assess the presence of a dose–response relationship between gestational hypertension and subsequent cardiovascular disease.

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Key Words: cardiovascular disease ■ gestational hypertension ■ pregnancy ■ review ■ women

Gestational hypertension (GH), also known as pregnancy-induced hypertension, is defined as the onset of high blood pressure (at least 140 mm Hg systolic or 90 mm Hg diastolic) without proteinuria on 2 occasions at least 4 hours apart in an ordinarily normotensive pregnant woman after 20 weeks of gestation. Rates of GH vary between countries, with 1% to 6% of pregnancies complicated by GH in Western countries.

Pregnancy-induced hypertension is increasingly recognized as a risk factor for subsequent cardiovascular disease (CVD) in women. In particular,
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pre-eclampsia, characterized by GH with proteinuria, is associated with a markedly higher CVD risk and has been incorporated in the American Heart Association guidelines for the assessment of CVD risk in women. It is unclear if GH and pre-eclampsia are manifestations of different severities of the same pathophysiological mechanism or represent separate pathologies. Therefore, the raised CVD risk in women with a history of pre-eclampsia may not be representative of the risk associated with GH.

Studies that have assessed the CVD risk associated with GH have found mixed results. Results have ranged from no raised risk to more than twice the risk of some cardiovascular events. This lack of clarity about the long-term cardiovascular risk for women who have had GH without proteinuria is further underscored by calls for further research into this area by the UK’s National Institute for Health and Care Excellence. Consequently, we conducted a systematic review and meta-analysis of prospective studies to evaluate the risk of a range of cardiovascular events for women after 1 or more pregnancies complicated by GH.

METHODS

The design, implementation, analysis, and reporting for this systematic review and meta-analysis are in accordance with the Meta-Analysis of Observational Studies in Epidemiology and Preferred Reporting Items for Systematic Reviews and Meta-Analyses protocols (Tables S1 and S2). An internal study protocol was developed to perform this review, which is registered on PROSPERO (https://www.crd.york.ac.uk/prospero/; review reference number CRD42018119031). The authors declare that all supporting data are available within the article and its online supplementary files.

Search Strategy and Selection Criteria

We searched the databases PubMed, Embase, and Web of Science in March 2019. No restrictions were applied to the language or publication period of the articles. Both medical search headings and open-text fields were used to identify articles.

The exposure was GH and any cardiovascular outcome was of interest, including (1) overall CVD; (2) coronary heart disease (CHD); (3) any stroke, including ischemic and hemorrhagic stroke; (4) heart failure; and (5) thromboembolic events. The details of the search terms are provided in Table S3. The search in PubMed was restricted to articles relating to humans. We cross-referenced the bibliographies of any relevant journal articles and systematic reviews we identified during our search to determine if there were any additional studies not found in our original search that fit our inclusion criteria.

To be included in the review, the articles had to compare the risk of at least 1 cardiovascular outcome for women with previous GH with that of women who had 1 or more normotensive pregnancies. GH was defined as a new onset of systolic and/or diastolic hypertension after 20 weeks gestation without proteinuria. Events had to occur more than 1 year postpartum to minimize the risk of comorbidity. Articles only evaluating pre-eclampsia, or combining both pre-eclampsia and GH as an exposure, were excluded to minimize heterogeneity in the exposure. Study designs were limited to cohort studies and case-control studies. Exclusion criteria were the following: (1) studies that included animals, men, children, or nulliparous women; (2) studies that did...
not have a cardiovascular outcome; (3) studies that combined women with GH and women with pre-eclampsia; and (4) studies that did not evaluate GH as an independent exposure.

Selection of Studies and Data Extraction
Using the software Abstracktr, each abstract found with our search strategy were screened by 2 authors (C.C.W.L., A.C.Q.L., S.H.L., G.F., B.C., O.B., B.M., or M.C.). Any differences between reviewers were discussed and resolved by a third individual (C.O.-W). For relevant abstracts, full texts were accessed to determine their eligibility for the review. Where 2 studies evaluated the same outcome in the same cohort, the study with the longer follow-up time was used. Data on the follow-up period, study design, population characteristics, sample size, exposure and outcome, methods of ascertainment for GH and cardiovascular events, and adjustment factors were abstracted and independently verified by a second author. Both minimally adjusted and fully adjusted measures of the association and 95% CIs were also extracted and verified. Any differences between reviewers were discussed and resolved by a third author.

For the fully adjusted measures of association, studies were categorized as poorly, adequately, or well adjusted. To be considered well adjusted, studies had to control for maternal age; socioeconomic factors; obstetric history, including pregnancy complications other than GH; and chronic diseases. We selected these categories as they broadly cover most potential confounders and are representative of the range of adjustments made in the studies included in the review. Adequately adjusted studies controlled for variables from 3 of these 4 categories, and poorly adjusted studies controlled for variables in 2 or fewer categories.

Two authors independently evaluated the bias within each individual study using the validated Newcastle–Ottawa Scale, a semiquantitative scale designed to evaluate the quality of nonrandomized studies. It allocates a maximum of 9 stars to a study. Study quality was judged on the selection criteria of participants, comparability of groups through adjustment, and exposure or outcome assessment.

Statistical Analysis
The included studies used 2 different approaches to classify GH exposure. The first approach classified women based on the presence or absence of a diagnosis of GH in the first pregnancy. The second approach classified women as having either a history of 1 or more pregnancies affected by GH or only having normotensive pregnancies. Because of the distinction between these 2 classifications, our meta-analyses were conducted assessing risk associated with 2 exposures: (1) a diagnosis of GH in the first pregnancy and (2) a history of 1 or more pregnancies affected by GH.

For a meta-analysis to be conducted, it was necessary to identify a minimum of 3 studies evaluating the risk of a particular cardiovascular outcome (eg, stroke, CHD) associated with 1 of these exposures. If fewer than 3 studies were found for an exposure–outcome combination, then the results were included in the systematic literature review, but not in the meta-analysis.

For studies that reported separate relative risk (RR) estimates for subgroups (eg ethnic groups) or that reported CHD and overall stroke risk estimates separately for the same population, but did not report an overall CVD risk estimate, we used inverse variance weighted fixed effects meta-analysis to generate overall study-level RRs before combining these results with those from other studies.

When pooling the results from separate studies, the inverse variance weighted method was used to combine odds ratio (OR), RR, and hazard ratios (HR) to produce a pooled RR under the rare outcome assumption. Random effects analyses using the DerSimonian–Laird model were used to allow for between-study heterogeneity as there were clear differences between the identified studies, such as ethnicity. Heterogeneity was assessed using the Cochrane $\chi^2$ statistic and the $I^2$ statistic. Individual RR estimates and summary estimates were displayed graphically with forest plots.

To assess the number of cases that could be avoided if effective intervention for CVD are targeted to women with GH, the absolute risk increases (ARI) for overall CVD and CHD were calculated separately for both exposures. The equation $\text{ARI}=(\text{RR}−1)\times(\text{assumed control risk})$ was used, where RR is from the meta-analysis.

Female-specific European Heart Network statistics for 2015 were used to estimate the assumed control risk (ie, the incidence) of overall CVD and CHD because the largest number of studies came from Europe. ARI were expressed as events per 1000 woman-years of follow-up. It was not possible to calculate the ARI for heart failure or thromboembolic events as we could not obtain estimates of their incidence. The ARI was not calculated for stroke because of the nonsignificant results in the main meta-analyses.

Sensitivity Analyses
A number of sensitivity analyses were conducted. The first analysis excluded studies with the largest effect estimates to assess the impact of these studies on the
magnitude of the pooled result and the observed heterogeneity. The second analysis included all studies and reran all meta-analyses with fixed effects models. This was performed because the DerSimonian–Laird method for random effects meta-analysis may have statistical limitations in the case of few studies. Therefore a fixed effects meta-analysis will provide an assessment of the consistency of the results and an estimation of the relationships specifically in the overall populations studied. Several studies assessed the risk of stroke subtypes (intracerebral hemorrhage and ischemic stroke) associated with a history of GH. To assess the risk of any stroke outcome, an additional meta-analysis was conducted that combined risk estimates for overall stroke and stroke subtypes associated with a history of GH.

A total of 5 stratified analyses were conducted to evaluate (1) the effect of different levels of adjustment, (2) the potential impact of bias in individual studies, and (3) the effect of study-level characteristics on the association between GH and overall CVD. Only overall CVD was assessed as an outcome because too few studies were included in the meta-analyses of other events. Analyses were stratified by (1) level of adjustment, (2) risk of bias, (3) duration of follow-up, (4) year of publication, and (5) the population studied. In these analyses, we tested for trend across strata using random effects meta-regression.

Small study effects were evaluated through funnel plots and Egger tests for meta-analyses including 6 or more studies. Upon evidence of funnel plot asymmetry and indication of significant bias from the Egger test, the trim-and-fill method was used to correct for funnel plot asymmetry.

All tests were 2-tailed and P values of <0.05 were considered statistically significant. STATA software package (version 14.2; Stata Corp, College Station, TX) was used for all statistical analyses.

**Figure 1.** Identification of studies included in the review of GH and risk of cardiovascular events.

GH indicates gestational hypertension.
RESULTS

Our search strategy identified 6974 studies, of which 6882 were excluded during the initial abstract screen. The remaining 92 articles were reviewed in full, resulting in 71 being excluded and 21 included in our final review (Figure 1). The studies included 3 601 192 women, with 127 913 women with a history of 1 or more pregnancies affected by gestational hypertension from 18 cohort studies\textsuperscript{11–13,29–39} and 3 nested case-control studies.\textsuperscript{15,18,40} Studies were conducted in Europe (12 studies) and North America (5 studies\textsuperscript{15,17,31,32,36} as well as in Taiwan (2 studies\textsuperscript{38,41}) and Australia (1 study\textsuperscript{15}) (Table).

All of the studies ascertained GH and cardiovascular events through medical records, registry data, or health insurance claims (Table, Table S4). The duration of follow-up varied from a median of 4.5 years\textsuperscript{16} to a maximum of 73 years\textsuperscript{17} (Table). Based on the Newcastle–Ottawa scale, 5 studies were judged to be at high risk of bias, and 10 studies provided risk estimates that were poorly adjusted (Tables S5 and S6).

GH in the First Pregnancy

A total of 11 studies,\textsuperscript{11,12,14,31,33,34,36–40} including 3 209 836 women (74 066 with GH), examined the risk of cardiovascular events in women whose first pregnancy was affected by GH. The risk of the following events was assessed: overall CVD, CHD, heart failure, any stroke, myocardial infarction (MI), thromboembolic events, angina, other circulatory disease, and a combined outcome of acute MI and acute cerebral stroke (Figure 2, Tables S7 and S8). Of the 9 included cohorts, GH affected 1.0% to 27.1% of first pregnancies. Meta-analyses included 2 818 819 women (66 130 with GH) for overall CVD, 1 793 887 women (35 281 with GH) for CHD, 1 402 870 women (27 940 with GH) for stroke, and 1 402 870 women (27 940 with GH) for thromboembolic events.

Meta-analyses of adjusted estimates found a significantly greater risk of overall CVD (7 studies\textsuperscript{11,12,14,31,33,34,36,37}: RR, 1.45; 95% CI, 1.17–1.80) and CHD (4 studies\textsuperscript{11,34,37,39}: RR, 1.46; 95% CI, 1.23–1.72), but not overall stroke (3 studies\textsuperscript{11,34,40}: RR, 1.26; 95% CI, 0.96–1.64) or thromboembolic events (3 studies\textsuperscript{11,34,40}: RR, 0.88; 95% CI, 0.73–1.07) (Figure 3). There was evidence of significant between-study heterogeneity for overall CVD (I\textsuperscript{2}=92%, P<0.001), CHD (74%, P=0.009), and overall stroke (82%, P=0.004), but not thromboembolic events (0%, P=0.413). Meta-analyses of the unadjusted results were consistent with these findings (Figure S1).

The ARI in overall CVD and CHD associated with GH in the first pregnancy, based on the European population, were 8.6 and 4.2 events per 1000 woman-years, respectively.

Five findings from 3 studies were not included in the meta-analyses (Table S8). These studies evaluated heart failure, a composite outcome of MI and acute cerebral stroke, angina, MI, and other circulatory disease. Greater risks of heart failure and combined acute MI and acute cerebral stroke were noted, which both attenuated after adjustment (adjusted HR, 1.37; 95% CI, 0.98–1.93; and adjusted HR, 1.8; 95% CI, 0.8–4.1), respectively.\textsuperscript{34,38} One study found no increased risk of MI (adjusted OR, 0.73; 95% CI, 0.32–1.63) or angina (adjusted OR, 1.02; 95% CI, 0.58–1.81), but noted a greater risk of other circulatory disease, defined as circulatory diseases that did not include hypertension, CHD, or cerebrovascular disease (adjusted incident rate ratio [IRR], 1.51; 95% CI, 1.06–2.14).\textsuperscript{40}

History of GH

A total of 11 studies from 10 populations\textsuperscript{1} assessed the risk of a cardiovascular outcome associated with a history of 1 or more pregnancies affected by GH. They included 2 291 304 women (73 994 with GH). The studies evaluated overall CVD, CHD, heart failure, overall stroke, intracerebral hemorrhage, ischemic stroke, MI, and thromboembolic events (Figure 1, Tables S7 and S8). Of the included studies, 9 were cohort studies in which the prevalence of women with a history of GH ranged from 1.1% to 19.0%. Meta-analyses included 861 087 women (50 356 with GH) for overall CVD, 471 454 women (35 272 with GH) for CHD, 1 126 452 women (16 800 with GH) for heart failure, and 463 911 women (34 281 with GH) for stroke.

In meta-analyses of adjusted risk estimates, a history of GH was associated with a greater risk of overall CVD (8 studies\textsuperscript{15–18,29,32}: RR, 1.81; 95% CI, 1.42–2.32), CHD (4 studies\textsuperscript{13,17,29,35}: RR, 1.83; 95% CI, 1.33–2.51) and heart failure (3 studies\textsuperscript{13,17,29}: RR, 1.77; 95% CI, 1.47–2.13), but not overall stroke (3 studies\textsuperscript{29,30,35}: RR, 1.50; 95% CI, 0.75–2.99) (Figure 4). There was evidence of high heterogeneity in all analyses: overall CVD (84%, P<0.001), CHD (88%, P<0.001), heart failure (63%, P=0.065), and overall stroke (70%, P=0.035). A greater CVD risk was also observed in the meta-analysis of unadjusted findings (Figure S2).

The ARI in overall CVD and CHD associated with a history of GH, based on the European population, were 15.6 and 7.6 events per 1000 woman-years, respectively.

Findings from 7 studies were not included in the meta-analysis (Table S8). These studies evaluated the risk of MI, intracerebral hemorrhage, ischemic stroke, cardiomyopathy, and thromboembolic events.

\textsuperscript{1}References 11, 12, 14, 16, 29, 30, 33–35, 37–39.

\textsuperscript{2}References 12, 13, 15–17, 29, 30, 32, 35, 41.
Table. Characteristics of Studies Included in the Review

| First Author, y | Details of Cohort | Study Design | Age at Enrollment, y | Duration of Follow-Up, y | No. of Women With GH | No. of Women | GH Definition | Method of GH Ascertainment | Outcome(s) | Method of Outcome Ascertainment | Method of Outcome Ascertainment |
|-----------------|-------------------|-------------|---------------------|--------------------------|----------------------|-------------|---------------|-----------------------------|------------|-------------------------------|-------------------------------|
| Andolf et al 2017 | Swedish National Register Study, 1973–2009 | Cohort study | Mean: 26.19 | Mean: 35 | 293,990 | 4,752 | ICD codes: ICD-8 | Medical records | Heart failure | Medical records | Medical records |
| Belkadi et al 2016 | Danish medical registries, 1978–2012 | Cohort study | Mean: 17.9 | Mean: 58 | 834,919 | 11,107 | ICD codes: ICD-8, ICD-10 | Medical records | Cardiomyopathy | Medical records | Medical records |
| Bhattacharya et al 2012 | Aberdeen Maternity and Neonatal Databank and NHS medical records, 1950–2008 | Cohort study | Max: 58 | Mean: 44–52 | 32,838 | 889 | ≥1 blood pressure reading of >140/90 mm Hg after 20 wk gestation | Medical records | CVD, CHD, stroke, pulmonary embolism | Medical records | Medical records |
| Cain et al 2016 | Florida maternal and infant databases, 1998–2009 | Cohort study | Median: 4.9 | Mean: 25.1 | 302,686 | 17,150† | ICD codes: ICD-9-CM | Medical records | CVD | Medical records | Medical records |
| Cirillo et al 2015 | US Child Health and Development Studies, 1959–2011 | Cohort study | Mean: 26.23 | Mean: 7.8 | 10,721 | 1,750† | ≥1 blood pressure reading of >140/90 mm Hg on two occasions at least four hours apart or one reading of >110/90 mm Hg | Medical records | CVD, thrombotic events | Medical records | Medical records |
| Grand et al 2017 | UK Clinical Database, 1986–2013 | Nesting Case Control | Mean: 7.2 | Mean: 4.7 | 103,000 | 16,000 | ICD codes: ICD-9-CM | Medical records | CVD | Birth certificate data | Birth certificate data |
| Ghezzi et al 2000 | Washington State Birth Events Record Database, 1987–2001 | Cohort study | Mean: 31.06 | Mean: 13 | 10,679 | 7,930 | ICD codes: ICD-9-CM | Medical records | CVD | Health insurance claims data | Health insurance claims data |
| Lin et al 2016 | Taiwanese National Health Insurance Database, 2000–2013 | Cohort study | Mean: 4.4 | Not given | 36,000 | 98 | ICD codes: ICD-9-CM | Medical records | CVD | Coding not specified | Medical records |
| Luo et al 2008 | Women giving birth in Helsinki hospitals, 1984–2006 | Cohort study | Mean: 26.0 | Mean: 12 | 5,000 | 400 | ICD codes: ICD-9-CM | Medical records | CVD | Coding not specified | Medical records |

(Continued)
| First Author, y | Details of Cohort | Study Design | No. of Women | No. of Women With GH | GH Definition | Method of GH Ascertainment | Duration of Follow-Up, y | Age at Enrollment, y | Outcome(s) | Method of Outcome Ascertainment |
|-----------------|-------------------|-------------|--------------|----------------------|--------------|-----------------------------|------------------------|---------------------|----------------|----------------------------------|
| Lykke et al 2009,34 | Danish medical registries, 1978–2007 | Cohort study | 782 287 | 7449 | ICD codes: ICD-8, ICD-10 | Medical records | Mean: 14.6 | Mean: 26.8 | CHD, heart failure, thromboembolic event, stroke | Medical records |
| Lykke et al 2010,33 | Danish medical registries, 1978–2007 | Cohort study | 782 287 | 7449 | ICD codes: ICD-8, ICD-10 | Medical records | Median: 14.8 | Mean: 26.8 | Fatal CVD | Medical records |
| Männistö et al 2013,15 | Northern Finland Birth Cohort, 1966–2000 | Cohort study | 7543 | 991 | SBP ≥145 mm Hg and/or DBP ≥95 mm Hg | Assessed during pregnancy as part of study | Mean: 39.4 | Mean: 26.76 | CHD, MI, heart failure, stroke | Medical records |
| Ray et al 2005,36 | Ontario Health Insurance Plan, 1990–2004 | Cohort study | 963 263 | 20 942 | ICD codes: ICD9 | Healthcare administrative databases | Median 8.7 | Mean: 28 | CVD | Hospital database |
| Riise et al 2018,37 | Norwegian registries, 1980–2009 | Cohort study | 587 755 | 11 600 | SBP ≥140 mm Hg, DBP ≥90 mm Hg, or >15 mm Hg BP increase measured <20 wk gestation | Medical records | Median: 14.3 | Mean: 26.3 | CVD, CHD, stroke | Medical records |
| Riise et al 2019,38 | Norwegian registries, 1980–2009 | Cohort study | 20 075 | 364 | SBP ≥140 mm Hg, DBP ≥90 mm Hg, or >15 mm Hg BP increase measured <20 wk gestation | Medical Records | Median: 11.4 | Mean: 26.0 | Composite: acute myocardial infarction or acute cerebral stroke | Medical records |
| Schmiegelow et al 2014,46 | Danish registries, 2004–2009 | Cohort study | 273 101 | 2903 | ICD codes: ICD-8, ICD-10 | Medical records | Median: 4.5 | Median: 30.4 | MI, ischemic stroke, CVD | Medical records |
| Theilen et al 2016,17 | Utah Population Database, 1939–2012 | Cohort study | 152 034 | 28 894 | Coding not specified | Birth certificates | Max: 73 | Mean: 26.0 | CHD, stroke | Medical records |
| Tooher et al 2017,13 | Royal Prince Alfred Women and Babies hospital, Australia, 1980–2009 onward | Cohort study | 27 887 | 625 | ICD codes: ICD-9-AM | Medical records | Median: 20 | Mean: 27 | CVD, CHD, stroke | Registry, discharge |
| Wikstrom et al 2005,39 | Swedish Medical Birth Register, 1987–2001 | Cohort study | 391 017 | 7936 | ICD codes: ICD-8 | Medical records | Max: 15 | Range: 15–64 | CHD | Registry (cause of death, hospital discharge) |

(Continued)
Evidence of higher risks were found for cardiomyopathy (HR, 1.83; 95% CI, 1.20–2.63), intracerebral hemorrhage (IRR, 3.62; 95% CI, 3.63–3.81) and, in 2 studies, ischemic stroke (IRR, 1.59; 95% CI, 1.24–2.04; HR, 2.78; 95% CI, 1.13–6.82).16,30,35,41 A history of GH was also associated with MI in 1 study (IRR, 1.75; 95% CI, 1.40–2.19),35 but not in a second study (HR, 1.41; 95% CI, 0.19–10.21).16 No statistically strong evidence of an association between a history of GH and thromboembolic events was found (HR, 1.5; 95% CI, 0.9–2.5).15

Two studies assessed the dose–response relationship between number of pregnancies with GH and a cardiovascular outcome. Both identified cohorts of women with 2 pregnancies who were categorized as having (1) GH in the first pregnancy only, (2) GH in the second pregnancy only, (3) GH in both pregnancies, or (4) GH in neither pregnancy. A greater risk of overall CVD relative to normotensive women was found for women with GH in the first pregnancy (HR, 1.7; 95% CI, 1.5–2.0), their second pregnancy (HR, 2.4; 95% CI, 2.1–2.8), and in both pregnancies (HR, 1.9; 95% CI, 1.8–2.0).37 A greater CHD risk was also noted for women with GH in either their first pregnancy (IRR, 1.9; 95% CI, 1.5–2.4) or second pregnancy (IRR, 2.4; 95% CI, 1.8–3.2) and for those with 2 or more affected pregnancies (IRR, 2.8; 95% CI, 2.0–3.9).39

Sensitivity Analyses
Risk estimates were consistent after excluding studies with the largest effect and after conducting a fixed effects meta-analysis, with I² results staying relatively constant (Table S9). When all stroke events, including overall stroke and stroke subtypes (intracerebral hemorrhage and ischemic stroke), were included in the history of GH...
meta-analysis, there was evidence for a greater risk of any stroke outcome for women with 1 or more pregnancies affected by GH: RR, 1.96 (95% CI, 1.06–3.63). Evidence for between-study heterogeneity was found in this analysis (98%, \( P < 0.001 \)) (Figure S3).

The overall CVD analyses were separately stratified by average duration of follow-up, risk of bias, level of adjustment, year of publication, and population (Table S10). There was no evidence that risk estimates varied between strata, and there remained evidence of heterogeneity in most categories after stratification.

**Small Study Effects**

The funnel plot for overall CVD risk after GH in the first pregnancy did not show evidence of asymmetry (Egger test, \( P = 0.935 \)) (Figure S4). The funnel plot for a history of GH and overall CVD risk indicated potential asymmetry (\( P = 0.051 \)), with publications of small studies with null or negative effect estimates missing (Figure S5). Use of the trim-and-fill method resulted in a RR of 1.26 (95% CI, 1.15–1.39). The funnel plot for a history of GH and risk of any stroke outcome did not show evidence of asymmetry (\( P = 0.382 \)) (Figure S6).

**DISCUSSION**

This systematic review found that women previously diagnosed with GH had a greater risk of overall CVD, CHD, and heart failure and some indication of a greater risk of stroke as well.
This study adds to the literature on the relationship between women’s obstetric history and risk of cardiovascular events. A single previous review evaluated cardiovascular events after GH; however, they focused on morbidity from CVD and cerebrovascular disease only. Our findings substantially build on it providing a comprehensive, holistic review of the risk of fatal and nonfatal cardiovascular events after GH.

**Strengths and Weaknesses of the Study**

Strengths of this study include the large number of women included and the variety of cardiovascular events assessed, which allowed us to obtain the most holistic picture to date of the effect of GH on long-term cardiovascular health. Because of the larger number of studies included in the overall CVD analysis, it was possible to assess the impact of study characteristics.

**Figure 4.** Association between a history of one or more pregnancies affected by gestational hypertension and subsequent risk of cardiovascular events in adjusted analyses. NG indicates not given; and RR, relative risk.
on the meta-analysis and to conduct sensitivity analyses. Furthermore, there was sufficient follow-up duration in many of the studies (10 studies had more than 15 years of follow-up) for long-term CVD risk to be adequately assessed. Lastly, diagnoses of GH and cardiovascular events were mainly ascertained through medical records, which reduced possible information bias arising from self-report.

Nevertheless, our study has limitations. First, it is possible that despite searching multiple databases without language or time restrictions, relevant studies were missed. Second, there were only 21 studies identified, and at most 8 studies were included in any single meta-analysis, suggesting that analyses could be influenced by a single study. However, exclusion of the studies with the largest effect estimates did not materially alter the conclusions of the meta-analyses. Few studies were found for some events, such as stroke and thromboembolic events, and thus limited sensitivity analyses.

Third, high heterogeneity ($I^2 > 70\%$) was found for most meta-analyses. This may be attributed to differences in study design, methodology, or population. Stratified analyses in the current review were limited to CVD only and may have been underpowered to detect some of these differences. Other potential sources of heterogeneity include differences in the frequency of postpartum chronic hypertension and variation in outcome and exposure identification. Chronic hypertension is likely to be an important mediator of the relationship between GH and CVD, therefore the frequency of conversion of GH to chronic hypertension may be a source of heterogeneity between populations and thus studies. Outcome definitions may have varied between studies because of the inclusion of different International Classification of Diseases (ICD) codes to define the same outcome (Table S4). Although all studies used robust measurements of exposure or events through blood pressure measurement and registries, revisions of ICD criteria could have led to differences in the definition of ICD codes between studies. Furthermore, there are challenges in identifying exposed women as well, as it requires a blood pressure measurement taken before 20 weeks gestation to rule out chronic hypertension, the criteria for which has changed over time, notably in the United States.

Fourth, many studies were of poor quality, and there were different adjustment sets considered, which could have resulted in residual confounding. However, when low-quality studies were excluded, the results were broadly similar. Fifth, our funnel plot for overall CVD risk with a history of GH indicates some asymmetry where small studies that report a significant, positive result are more likely to be published (Figure S4). Use of the trim-and-fill method found that the association would remain after correcting for the asymmetry. Lastly, the majority of studies were from Western populations, which may limit the generalizability of these findings to other populations.

Implications for Clinical Practice
Several theories have been proposed to explain the link between GH and the development of CVD. Hypertension in pregnancy may cause lasting damage that contributes to CVD. Alternatively, or in addition to this, women who develop GH may have a pre-existing predisposition to CVD, which unmasks itself during pregnancy. For example, prepregnancy body mass index is particularly important for GH risk, and body mass index, in general, is linked to CVD development. These theories, in combination with the findings of this review, underscore the importance of intervention to decrease CVD risk factors. This could have the dual benefit of decreasing both the severity and incidence of GH and CVD.

The timing of when an intervention is administered merits discussion, and the pathological mechanisms linking GH to CVD development have implications for this. If there is a pre-existing predisposition to CVD, then intervention before conception should be a priority. There is increasing emphasis on the importance of preconception health and its implications for future health. However, the challenges of intervening before conception lie in identifying women considering pregnancy and will not aid women with unplanned pregnancies, which may be up to half of all pregnancies in some groups of women.

Intervention during or shortly after pregnancy may be a viable approach and may help mitigate any long-term damage caused by GH. Strategies for managing cardiovascular risk factors during pregnancy could include lifestyle changes that limit excess gestational weight gain, a known risk factor for GH and other pregnancy complications. There is evidence that lifestyle changes can be effective in mitigating maternal and fetal risks, and research is underway to identify the ideal interventions. Women who experience GH may also benefit from counseling during and/or after pregnancy about their long-term cardiovascular risk. Strategies that could be implemented after pregnancy may include discussion of heart age calculations, which may be more applicable to a younger population of women than predicting their cardiovascular risk, which is likely to be low in the years after giving birth.

Unanswered Questions and Future Research
Pre-eclampsia is currently recognized in guidelines for assessing CVD risk in women; however, GH is not. To assess whether GH should also be included in CVD risk guidelines, further research is needed.
The risk of some diseases that have been evaluated in relation to GH, such as stroke subtypes, would benefit from further study to confirm the association indicated in this review, whereas many cardiovascular events have been entirely overlooked, such as peripheral arterial disease and transient ischemic attack. Furthermore, only 2 studies were identified that assessed a dose–response relationship, that is, whether the risk of a cardiovascular outcome rises with an increasing number of pregnancies affected by GH. Given the evidence for a dose–response relationship for both preterm birth and pre-eclampsia, whereby CVD risk is greater with the number of affected pregnancies,\(^\text{50,61}\) the limited evaluation of a dose–response relationship for GH needs addressing.

**CONCLUSIONS**

In conclusion, we found that GH is associated with a greater risk of overall CVD, specifically CHD and heart failure. The greater risk associated with many of these events is similar to other pregnancy complications, such as preterm birth and fetal growth restriction. Women who experience GH should be aware of this greater risk and may benefit from prenatal and postnatal counseling to increase their awareness of strategies that can reduce their CVD risk during and after birth.

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Supplemental Material
| Section/topic | # | Checklist item                                                                                                                                                                                                 | Reported on page # |
|---------------|---|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|
| TITLE         |   | **Title** 1  Identify the report as a systematic review, meta-analysis, or both.                                                                                                                                 | 1                 |
| ABSTRACT      |   | **Structured summary** 2  Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 2                 |
| INTRODUCTION  |   | **Rationale** 3  Describe the rationale for the review in the context of what is already known.                                                                                                                                 | 3                 |
|               |   | **Objectives** 4  Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 3                 |
| METHODS       |   | **Protocol and registration** 5  Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | 3                 |
|               |   | **Eligibility criteria** 6  Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 3                 |
|               |   | **Information sources** 7  Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 3                 |
|               |   | **Search** 8  Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.                                                                 | 3                 |
|               |   | **Study selection** 9  State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 3-4               |
|               |   | **Data collection process** 10  Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 4                 |
|               |   | **Data items** 11  List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.                                                                 | 4                 |
|               |   | **Risk of bias in individual studies** 12  Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 4                 |
|               |   | **Summary measures** 13  State the principal summary measures (e.g., risk ratio, difference in means).                                                                                                         | 4                 |
| Section                      | Item | Description                                                                                   | Pages |
|------------------------------|------|-----------------------------------------------------------------------------------------------|-------|
| Synthesis of results         | 14   | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., \( I^2 \)) for each meta-analysis. | 4     |
| Risk of bias across studies  | 15   | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 5     |
| Additional analyses          | 16   | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | 4-5   |
| RESULTS                      |      |                                                                                               |       |
| Study selection              | 17   | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 5, Fig 1 |
| Study characteristics        | 18   | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | 5, 9-13, Tables S4, S5 & S7 |
| Risk of bias within studies  | 19   | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | Tables S6 & S10 |
| Results of individual studies| 20   | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | Table S8 & S9, Fig 3 & 4 Fig S1, S2 & S3 |
| Synthesis of results         | 21   | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | Fig 2, 3 & 4 Fig S1, S2 & S3 |
| Risk of bias across studies  | 22   | Present results of any assessment of risk of bias across studies (see Item 15). | 5, 7, Table S11, Fig S4, S5 & S6 |
| Additional analysis          | 23   | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | 6-7, Table S9 & S10 |
| DISCUSSION                   |      |                                                                                               |       |
| Summary of evidence          | 24   | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 7-9   |
| Limitations                  | 25   | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 8     |
| Conclusions                  | 26   | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 7-9   |
| FUNDING                      |      |                                                                                               |       |
| Funding                      | 27   | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 1     |
### Table S2. MOOSE Checklist for Meta-analyses of Observational Studies.

| Item No | Recommendation | Reported on Page No |
|---------|----------------|---------------------|
| 1       | Problem definition | 3                   |
| 2       | Hypothesis statement | 3                   |
| 3       | Description of study outcome(s) | 3                   |
| 4       | Type of exposure or intervention used | 3                   |
| 5       | Type of study designs used | 3                   |
| 6       | Study population | 3                   |
| 7       | Qualifications of searchers (eg, librarians and investigators) | 4                   |
| 8       | Search strategy, including time period included in the synthesis and key words | 3                   |
| 9       | Effort to include all available studies, including contact with authors | 3                   |
| 10      | Databases and registries searched | 3                   |
| 11      | Search software used, name and version, including special features used (eg, explosion) | 3-4                 |
| 12      | Use of hand searching (eg, reference lists of obtained articles) | 3                   |
| 13      | List of citations located and those excluded, including justification | Figure 1            |
| 14      | Method of addressing articles published in languages other than English | None found          |
| 15      | Method of handling abstracts and unpublished studies | None found          |
| 16      | Description of any contact with authors | None required       |
| 17      | Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested | 5                   |
| 18      | Rationale for the selection and coding of data (eg, sound clinical principles or convenience) | 4                   |
| 19      | Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability) | 4                   |
| 20      | Assessment of confounding (eg, comparability of cases and controls in studies where appropriate) | 4, Table S5         |
| 21      | Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results | 4, Table S4, Table S9 |
| 22      | Assessment of heterogeneity | 4                   |
| 23      | Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated | 4                   |
| 24      | Provision of appropriate tables and graphics | Fig 1, Tables S1-S7 |
| 25      | Graphic summarizing individual study estimates and overall estimate | Fig 2-4, Fig S1, S2 |
| 26      | Table giving descriptive information for each study included | Table S4, S5, S7    |
|   |   |   |
|---|---|---|
| 27 | Results of sensitivity testing (eg, subgroup analysis) | 7, Table S10-S11, Fig S3 |
| 28 | Indication of statistical uncertainty of findings | Fig 2-4, Fig S1, S2 |
|   | Reporting of discussion should include |   |
| 29 | Quantitative assessment of bias (eg, publication bias) | 8, Fig S4-S6 |
| 30 | Justification for exclusion (eg, exclusion of non-English language citations) | n/a |
| 31 | Assessment of quality of included studies | 8, Table S6-S7 |
|   | Reporting of conclusions should include |   |
| 32 | Consideration of alternative explanations for observed results | 8-9 |
| 33 | Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review) | 8 |
| 34 | Guidelines for future research | 9 |
| 35 | Disclosure of funding source | 1 |
| Population | (“humans”[MeSH Terms] OR "Women"[Mesh] OR "Female"[Mesh] OR "Pregnancy"[Mesh]) AND ("Hypertension, Pregnancy-Induced"[Mesh] OR "Gestational hypertension"[All Fields] OR "Pregnancy Induced Hypertension"[All Fields] OR "Transient Hypertension" in Pregnancy[All Fields]) AND |
|-----------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Exposure  | ("Acute Coronary Syndrome"[All Fields] OR "Aneurysm"[All Fields] OR "Angina"[All Fields] OR "Aortic Stenosis"[All Fields] OR "Aortic Stenoses"[All Fields] OR "Aortic Valve Insufficiency"[All Fields] OR "Aortic Valve Stenosis"[All Fields] OR "Aortic Valve Stenoses"[All Fields] OR "Arrhythmia"[All Fields] OR "Atrial Fibrillation"[All Fields] OR "Atrial Flutter"[All Fields] OR "Bradyarrhythmia"[All Fields] OR "Cardiac Arrest"[All Fields] OR "Cardiac Oedema"[All Fields] OR "Cardiac edema"[All Fields] OR "Cardiac Tamponade"[All Fields] OR "Cardiomegaly"[All Fields] OR "Cardiomyopathy"[All Fields] OR "Coronary Cardiovascular Disease"[All Fields] OR "CVD"[All Fields] OR "Cerebrovascular Disease"[All Fields] OR "Cerebrovascular Disorder"[All Fields] OR "Cerebral infarction"[All Fields] OR "Cerebral haemorrhage"[All Fields] OR "Cerebral hemorrhage"[All Fields] OR "Commotio Cordis"[All Fields] OR "Coronary Artery Disease"[All Fields] OR "Coronary Disease"[All Fields] OR "CHD"[All Fields] OR "Coronary Occlusion"[All Fields] OR "Coronary Restenosis"[All Fields] OR "Coronary Restenoses"[All Fields] OR "Coronary Stenosis"[All Fields] OR "Coronary Stenoses"[All Fields] OR "Coronary Vasospasm"[All Fields] OR "Emboli"[All Fields] OR "Emboli"[All Fields] OR "Endocarditis"[All Fields] OR "Heart Arrest"[All Fields] OR "Heart Attack"[All Fields] OR "Heart Block"[All Fields] OR "Heart Disease"[All Fields] OR "Heart Failure"[All Fields] OR "Heart Rupture"[All Fields] OR "Heart Valve Disease"[All Fields] OR "Heart Valve Prolapse"[All Fields] OR "Hypertroph"[All Fields] OR "Intracranial Haemorrhage"[All Fields] OR "Intracranial Hemorrhage"[All Fields] OR "Long QT Syndrome"[All Fields] OR "Mitra Valve Insufficiency"[All Fields] OR "Myocardial Infarction"[All Fields] OR "Myocardial Ischaemia"[All Fields] OR "Myocardial Ischaemia"[All Fields] OR "Myocardial Ischaemia"[All Fields] OR "Myocardial Ischaemia"[All Fields] OR "Myocardial Ischaemia"[All Fields] OR "Myocardial Ischaemia"[All Fields] OR "Myocardial Reperfusion Injury"[All Fields] OR "Myocardial Stunning"[All Fields] OR "Paroxysmal Dyspnea"[All Fields] OR "Peripheral arterial disease"[All Fields] OR "Pre-Excitation Syndrome"[All Fields] OR "Pulmonary Valve Insufficiency"[All Fields] OR "Pulmonary Valve Stenosis"[All Fields] OR "Pulmonary Heart Disease"[All Fields] OR "Stroke"[All Fields] OR "Sudden Cardiac Arrest"[All Fields] OR "Subarachnoid haemorrhage"[All Fields] OR "Subarachnoid hemorrhage"[All Fields] OR "Tachycardia"[All Fields] OR "Thrombosis"[All Fields] OR "Thromboses"[All Fields] OR "Transient Ischaemic Attack"[All Fields] OR "Transient Ischemic Attack"[All Fields] OR "Tricuspid Valve Insufficiency"[All Fields] OR "Tricuspid Valve Stenosis"[All Fields] OR "Tricuspid Valve Stenoses"[All Fields] OR "Ventricular Dysfunction"[All Fields] OR "Ventricular Fibrillation"[All Fields] OR "Ventricular Flutter"[All Fields] OR "Acute Coronary Syndrome"[Mesh] OR "Aneurysm"[Mesh] OR "Angina Pectoris"[Mesh] OR "Aortic Valve Stenosis"[Mesh] OR "Aortic Valve Insufficiency"[Mesh] OR "Arrhythmias, Cardiac"[Mesh] OR "Atrial Fibrillation"[Mesh] OR "Atrial Flutter"[Mesh] OR "Bradyarrhythmia, Cardiac"[Mesh] OR "Heart Arrest"[Mesh] OR "Edema, Cardiac"[Mesh] OR "Cardiac Tamponade"[Mesh] OR "Cardiomegaly"[Mesh] OR "Cardiomyopathies"[Mesh] OR "Cardiovascular Diseases"[Mesh] OR "Cerebrovascular Disorders"[Mesh] OR "Commotio Cordis"[Mesh]) OR "Coronary Artery Disease"[Mesh] OR "Coronary Disease"[Mesh] OR "Coronary Occlusion"[Mesh] OR "Coronary Restenosis"[Mesh] OR "Coronary Stenosis"[Mesh] OR "Coronary Stenoses"[Mesh] OR "Coronary Vasospasm"[Mesh] OR "Emboli"[Mesh] OR "Endocarditis"[Mesh] OR "Myocardial Infarction"[Mesh] OR "Heart Block"[Mesh] OR "Heart Disease"[Mesh] OR "Heart Failure"[Mesh] OR "Heart Rupture"[Mesh] OR "Heart Valve Disease"[Mesh] OR "Heart Valve Prolapse"[Mesh] OR "Hypertroph"[Mesh] OR "Intracranial Hemorrhage"[Mesh] OR "Intracranial Hemorrhage"[Mesh] OR "Long QT Syndrome"[Mesh] OR "Mitra Valve Insufficiency"[Mesh] OR "Myocardial Ischaemia"[Mesh] OR "Myocardial Reperfusion Injury"[Mesh] OR "Myocardial Stunning"[Mesh] OR "Dyspnea, Paroxysmal"[Mesh] OR "Peripheral Arterial Disease"[Mesh] OR "Pre-Excitation Syndromes"[Mesh] OR "Pulmonary Valve Insufficiency"[Mesh] OR "Pulmonary Valve Stenosis"[Mesh] OR "Pulmonary Valve Stenoses"[Mesh] OR "Pulmonary Heart Disease"[Mesh] OR "Stroke"[Mesh] OR "Death, Sudden, Cardiac"[Mesh] OR "Subarachnoid Hemorrhage"[Mesh] OR "Tachycardia"[Mesh] OR "Thrombosis"[Mesh] OR "Ischemic Attack, Transient"[Mesh] OR "Tricuspid Valve Insufficiency"[Mesh] OR "Tricuspid Valve Stenosis"[Mesh] OR "Ventricular Dysfunction"[Mesh] OR "Ventricular Fibrillation"[Mesh] OR "Ventricular Flutter"[Mesh]) AND |

| Study Design | ("longitudinal studies"[MeSH Terms] OR "longitudinal study"[All Fields] OR "longitudinal studies"[All Fields] OR "prospective"[All Fields] OR "cohort"[All Fields] OR "cohorts"[All Fields] OR "follow up"[All Fields] OR "follow-up"[All Fields] OR "Epidemiology"[Mesh] OR "Epidemiology"[All Fields] OR "Epidemiological"[All Fields] OR "Retrospective Studies"[Mesh] OR "Retrospective"[All Fields] OR "prospective"[All Fields] OR "Cross-Sectional Studies"[Mesh] OR "Cross-Sectional"[All fields] OR "Case-Control Studies"[Mesh] OR "Case-Control"[All Fields]) AND |

**Table S3. PubMed Search Strategy.**
Table S4. Definitions of Cardiovascular Events.

| First author, year | Definition |
|---------------------|-----------|
| Andolf et al. 2017  | Coronary Heart Disease: ICD-10 (I20-25) |
|                     | Stroke: ICD-10 (I60-69) |
|                     | Heart Failure: ICD-10 (I50) |
| Behrens et al. 2016 | Congestive Heart Failure: ICD-10 (I20-25, 782.49); ICD-10 (I50.0-50.9) |
|                     | Cardiomyopathy: ICD-8 (425.99); ICD-10 (I42.0-43.8, O90.3) |
| Bhattacharya et al. | CHD: ICD-8 (410); ICD-10 (I20) |
| 2012                | Stroke: ICD-8 (430); ICD-10 (I60-9) |
|                     | CVD: ICD-8 (410, 411, 414, 429); ICD-10 (I20, I21, I24, I25) |
| Cain et al. 2016    | CVD: ICD-9 codes for CHD, cerebrovascular disease, or cardiac or peripheral arterial revascularization that were not specified |
| Cirillo et al. 2015 | CVD mortality: ICD-7 (420.1); ICD-8 (410, 412); ICD-9 (410, 411, 414, 429), ICD-10 (I21, I24, I25) |
| Grandi et al. 2017  | CVD: Read codes for cerebrovascular disease, CHD, coronary artery revascularization, MI, peripheral arterial disease, transient ischaemic attack and stroke |
| Kestenbaum et al.   | Thromboembolism: ICD-9 (451, 453, 415.1); ICD-10 (I60-61, I63-64, except I63.6) |
| 2003                | CVD: ICD-9 (410, 430, 431, 434, 436), coronary artery revascularization procedure, including coronary artery bypass grafting (procedure code:36) |
| Lin et al. 2016     | Intracerebral haemorrhage: ICD-9 (430–432) |
| Luoto et al. 2008   | CVD: ICD-9 (389-459); ICD-10 (I00-I99) |
| Lykke et al. 2009   | CHD: ICD-8 (410-414), ICD-10 (I20-I25) |
|                     | Heart Failure: ICD-8 (42709-42711, 42719, 42799, 42899, 42900, 42908, 42909), ICD-10 (I50, I51.3, I51.9) |
|                     | Thromboembolic event: ICD-8 (444, 450-1), ICD-10 (I26, I74, I82) |
| Lykke et al. 2010   | Stroke: ICD-8 (430-438), ICD-10 (I60-I67, G45) |
| Männistö et al. 2013| CVD: ICD-8 (39-44, 451-458), ICD-10 (D10-D19) |
| Ray et al. 2005     | CHD, MI, Heart failure, Ischemic stroke: ICD codes, which were not specified |
| Riise et al. 2018   | CVD: ICD-9, ICD-10 codes, which were not specified |
| Riise et al. 2019   | Acute MI or acute cerebral stroke - composite of hospitalization with AMI: ICD-9 (410); ICD-10 (I21-22); death from CHD: ICD-9 (410-414), ICD-10 (I20-25); hospitalization or death with acute cerebral stroke: ICD-9 (43), ICD-10 (I60-61, I63-64, except I63.6) |
| Study                        | Description                                                                 |
|------------------------------|-----------------------------------------------------------------------------|
| Schmiegelow et al. 2014[16]  | MI: ICD-10 (I21-I22); CVD: ICD-10 (I00-I99); Ischemic stroke: ICD-10 (I63-I64). |
| Theilen et al. 2016[17]      | CVD: ICD-9 (390–459); CHD, Stroke: Codes not specified                      |
| Tooher et al. 2017[13]       | CHD, Stroke: ICD-9 & ICD-10 codes, which weren’t specified                  |
| Wikstrom et al. 2005[40]     | CHD: ICD-9 (410–414), ICD-10 (I20–I25)                                      |
| Wilson et al. 2003[41]       | Angina, MI, DVT: ascertained through the women’s general practitioner, medical and death records. Other circulatory disease: ICD-9 (390-8, 405, 415-27, 440-59), ICD-10 (I00-9, I15, I26-8, I30-49, I51-2, I70-99) |
| Yeh et al. 2014[18]          | CVD, ICD-9 (390-459)                                                        |

CHD – coronary heart disease; CVD – cardiovascular disease; ICD – International classification of diseases; MI – myocardial infarction
Table S5. Risk of Bias Assessment in Prospective Studies.

| First author, year | Selection | Comparability | Outcome | Overall Assessment |
|--------------------|-----------|---------------|---------|--------------------|
| Andolf et al. 2017 30 | ★★★ | ★ | ★ | Low Risk of Bias |
| Behrens et al. 201631 | ★★★★ | ★ | ★★★ | Low Risk of Bias |
| Bhattacharya et al. 201211 | ★★★ | ★ | ★ | Low Risk of Bias |
| Cain et al. 201632 | ★★★★ | ★ | ★ | Low Risk of Bias |
| Cirillo et al. 201533 | ★★★★ | ★ | ★ | Low Risk of Bias |
| Grandi et al. 201714 | ★★★★ | ★ | ★ | Low Risk of Bias |
| Kestenbaum et al. 2003 15 | ★★★★ | ★ | ★ | High Risk of Bias |
| Lin et al. 201629 | ★★★★ | ★ | ★ | High Risk of Bias |
| Luoto et al. 200812 | ★★ | ★★ | ★★ | Moderate Risk of Bias |
| Lykke et al. 200935 | ★★★★ | ★ | ★ | Low Risk of Bias |
| Lykke et al. 201034 | ★★★★ | ★ | ★ | Low Risk of Bias |
| Männistö et al. 201336 | ★★★ | ★ | ★ | Low Risk of Bias |
| Ray et al. 200537 | ★★★★ | ★ | ★ | Low Risk of Bias |
| Riise et al. 201838 | ★★★★ | ★ | ★★★ | Low Risk of Bias |
| Riise et al. 201939 | ★★★★ | ★ | ★★★ | Low Risk of Bias |
| Schmiegelow et al. 201416 | ★★★★ | ★ | ★ | Low Risk of Bias |
| Theilen et al. 201617 | ★★★★ | ★ | ★ | High Risk of Bias |
| Tooher et al. 201713 | ★★★ | ★ | ★ | High Risk of Bias |
| Wikstrom et al. 200540 | ★★★★ | ★ | ★ | Low Risk of Bias |
| Wilson et al. 200341 | ★★★ | ★ | ★ | Low Risk of Bias |
| Yeh et al. 201418 | ★★★★ | ★ | ★ | Low Risk of Bias |

Acceptable loss of follow-up taken to be <10%; Sufficient duration of follow-up taken to be from average age at pregnancy to after menopause (52 years old)
| First author, year | Adjustment factors                                                                                                                                                                                                 | Quality of adjustment |
|--------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| Andolf et al. 2017 | Mother's age at birth, mother's attained educational level in 1985, marital status and origin (Nordic/non-Nordic), history of cardiovascular disease later in life (diabetes, arteriosclerosis, stroke, ischemic heart disease, heart failure and hypertension) | Adequate              |
| Behrens et al. 2016 | Maternal age, maternal birth year, parity, multiple pregnancy and stillbirth                                                                                                                                         | Poor                  |
| Bhattacharya et al. 2012 | Year of birth, social class and smoking                                                                                                                                                                                 | Poor                  |
| Cain et al. 2016   | Age, race/ethnicity, nativity, education, income, 5-year history of hyperlipidemia, migraine, lupus; pre-pregnancy BMI, gestational diabetes, tobacco use, drug use, and infant sex                                               | Well                  |
| Cirillo et al. 2015 | Age, race, parity, BMI, and cigarette smoking                                                                                                                                                                        | Well                  |
| Grandi et al. 2017 | Age, smoking, BMI, excessive alcohol use, year of cohort entry, region of residence, multiple gestation at first pregnancy, depression, dyslipidaemia, venous thromboembolism, polycystic ovary syndrome, gestational diabetes (measured between 12 weeks of gestation and 6 weeks post-partum), diabetes mellitus, renal disease, migraines, family history of hypertension and family history of cardiovascular disease any time before cohort entry, number of distinct drug classes prescribed, and use of statin, aspirin and anti-depressant medications in the year prior to pregnancy | Well                  |
| Kestenbaum et al. 2003 | Age, parity, calendar year of delivery                                                                                                                                                                                   | Poor                  |
| Lin et al. 2016    | Age, follow-up years                                                                                                                                                                                                   | Poor                  |
| Luoto et al. 2008  | Age, hormone use, height, marital status and visit to private doctor                                                                                                                                                  | Adequate              |
| Lykke et al. 2009  | Age, year of delivery, preterm delivery, SGA offspring, placental abruption, stillbirth and later type 2 diabetes mellitus                                                                                                                                                   | Adequate              |
| Lykke et al. 2010  | Age, year of delivery.                                                                                                                                                                                                  | Poor                  |
| Männistö et al. 2013 | Age at pregnancy, pre-pregnancy BMI, smoking, parity, diabetes mellitus before/during pregnancy, socioeconomic status                                                                                             | Well                  |
| Ray et al. 2005    | Age, multiple gestation, length of stay, income quintile, rural residence, drug dependence, and gestational diabetes mellitus in index delivery, and hypertension, any diabetes mellitus, obesity, dyslipidaemia, tobacco use, renal disease, migraine headache, and systemic lupus erythematosus | Well                  |
| Riise et al. 2018  | Age, educational level, marital status, and birth year of first child                                                                                                                                                   | Poor                  |
| Riise et al. 2019  | Age at recruitment age at first delivery, education (primary, high school/vocational, any college/university) and a family history of MI prior to age 60                                                                  | Well                  |
| Schmiegelow et al. 2014 | Age, smoking, and year of inclusion                                                                                                                                                                                  | Poor                  |
| Theilen et al. 2016 | Age, year of childbirth, parity, infant sex, parental education, preterm delivery, race-ethnicity, maternal marital status                                                                                           | Adequate              |
| Tooher et al. 2017 | Age, gestation, and parity                                                                                                                                                                                               | Poor                  |
| Study                          | Variables                                                                 | Adequacy   |
|-------------------------------|---------------------------------------------------------------------------|------------|
| Wikstrom et al. 2005          | Age, socio-economic level and category of hospital                        | Poor       |
| Wilson et al. 2003 *          | Age, BMI, social class, and smoking habit                                 | Adequate   |
| Yeh et al. 2014               | Age, diabetes, dyslipidemia, incident hypertension, date of delivery      | Poor       |

* Risk estimates for "other circulatory disease" were adjusted for age at delivery and social class only, and is considered poorly adjusted.
Table S7. Results of Studies Included in the Meta-analysis by Outcome.

| Outcome          | First author, year | Exposure definition | Cases (N) | Point Estimate | Unadjusted or Age-adjusted Results | Adjusted Results * |
|------------------|--------------------|---------------------|-----------|----------------|-----------------------------------|--------------------|
| Cardiovascular Disease |                    |                     |           |                |                                   |                    |
|                  | Behrens et al. 2016$^{11}$ | GH in 1st pregnancy | 1,319     | IRR            | 1.19 (1.06,1.34) | 1.25 (1.11,1.41) |
|                  | Cain et al. 2016$^{32}$ | GH in 1st pregnancy | 2,447     | HR             | 1.18 (1.01,1.37) | 0.99 (0.85, 1.16) |
|                  | Grandi et al. 2017$^{14}$ | GH in 1st pregnancy | 920 †     | HR             | 2.4 (1.9, 3.1)   | 2.3 (1.8, 2.9)     |
|                  | Luoto et al. 2008$^{12}$ | GH in 1st pregnancy | 38        | HR             | 0.87 (0.61,1.25) | 0.90 (0.62, 1.30) |
|                  | Lykke et al. 2009     | GH in 1st pregnancy | 1,194     | HR             | NG                  | 2.47 (1.74, 3.52)   |
|                  | Schmiegelow et al. 2014 | A history of GH    | 9,000 †   | HR             | Nigerian: 1.62 (1.36,1.92) | 1.70 (1.52, 1.93)   |
|                  |                      |                     |           |                | African American: 1.70 (1.10,2.65) | 1.30 (1.28, 1.34)   |
|                  |                      |                     |           |                | non-African American: 0.90 (0.63,1.36) | 0.87 (0.68, 1.09)   |
|                  |                      |                     |           |                |                                   |                    |
| Coronary Heart Disease |                    |                     |           |                |                                   |                    |
|                  | Behrens et al. 2016$^{11}$ | GH in 1st pregnancy | 681       | IRR            | 1.09 (1.00,1.19) | 1.22 (1.11, 1.34) |
|                  | Lykke et al. 2009$^{35}$ | GH in 1st pregnancy | 2,271     | HR             | 1.67 (1.41,1.97) | 1.48 (1.25, 1.76)   |
|                  | Riise et al. 2018$^{38}$ | GH in 1st pregnancy | 2,364     | HR             | 1.7 (1.3, 2.2)   | 1.7 (1.3, 2.1)     |
|                  | Wikstrom et al. 2005$^{40}$ | GH in 1st pregnancy | 2,142     | IRR            | 2.0 (1.7, 2.5)   | 1.6 (1.3, 2.0)     |
|                  | Andolf et al. 2017$^{30}$ | A history of GH    | 10,755 †  | HR             | 1.33 (1.20,1.48) | 1.26 (1.13, 1.40)   |
|                  | Männistö et al. 2013$^{36}$ | A history of GH    | 1,225     | HR             | NG                  | 1.44 (1.24, 1.68)   |
|                  | Tooher et al. 2017$^{13}$ | A history of GH    | 3,19      | OR             | NG                  | 3.19 (2.11, 4.83)   |
|                  | Theilen et al. 2016$^{17}$ | A history of GH    | 182       | HR             | NG                  | 2.77 (1.62, 4.75)   |
|                  |                      |                     |           |                |                                   |                    |
| Stroke $^1$       | Behrens et al. 2016$^{11}$ | GH in 1st pregnancy | 2,638     | IRR            | 0.97 (0.86,1.09) | 1.04 (0.91,1.18)   |
|                  | Lykke et al. 2009$^{35}$ | GH in 1st pregnancy | 8,987     | HR             | 1.68 (1.42,1.97) | 1.51 (1.26, 1.81)   |
|                  | Riise et al. 2018$^{38}$ | GH in 1st pregnancy | 2,452     | HR             | 1.3 (0.9, 1.7)   | 1.3 (0.9, 1.7)     |
|                  | Andolf et al. 2017$^{30}$ | A history of GH    | 7,436 †   | HR             | 1.36 (1.20,1.55) | 1.30 (1.14, 1.48)   |
|                  | Tooher et al. 2017$^{13}$ | A history of GH    | NG        | OR             | NG                  | 0.57 (0.14, 2.31)   |
|                  | Theilen et al. 2016$^{17}$ | A history of GH    | NG        | HR             | NG                  | 2.97 (1.49, 5.92)   |
| Heart Failure     | Andolf et al. 2017$^{30}$ | A history of GH    | 3,165 †   | HR             | 1.62 (1.36,1.93) | 1.52 (1.28, 1.80)   |
|                  | Männistö et al. 2013$^{36}$ | A history of GH    | 486       | IRR            | NG                  | 1.79 (1.43, 2.21)   |
|                  | Behrens et al. 2016$^{51}$ | A history of GH    | 3,581     | HR             | NG                  | 2.07 (1.70, 2.52)   |
| Study                      | Condition                        | N   | Measure | Estimate (CI)       | IRR  (CI)   |
|----------------------------|----------------------------------|-----|---------|---------------------|------------|
| Bhattacharya et al. 2012   | GH in 1st pregnancy              | 384 | IRR     | 0.82 (0.65, 1.04)   | 0.86 (0.67, 1.09) |
| Lykke et al. 2009          | GH in 1st pregnancy              | 3,881 | HR     | 1.01 (0.72 - 1.40)  | 1.03 (0.73, 1.45)   |
| Wilson et al. 2003         | GH in 1st pregnancy              | 47  | OR      | NG                  | 0.65 (0.35, 1.20)  |

GH – gestational hypertension; NG – not given; HR – Hazard Ratio, OR – Odds Ratio, IRR – incident rate ratio

* See Table S4 for adjustment; † estimated; ‡ Results were combined by fixed effect meta-analysis to provide an estimate of the CVD risk for the whole population.

§ CHD and stroke results for each paper were combined by fixed effect meta-analysis to provide an estimate of the risk of CVD. † Studies that reported all-cause stroke only. ‡ Study specific outcomes were: Wilson – Deep Vein Thrombosis, Bhattacharya - Pulmonary Embolism; Lykke – Thromboembolic Events
| Outcome | First author, year | Exposure definition | Cases (N) | Point Estimate | Unadjusted Results | Adjusted Results * |
|---------|--------------------|---------------------|-----------|----------------|------------------|------------------|
| Heart Failure | Lykke et al 2009 | GH in 1st pregnancy | 7,483 | HR | 1.57 (1.12-2.20) | 1.37 (0.98-1.93) |
| Angina | Wilson et al. 2003 | GH in 1st pregnancy | 64 | OR | NG | 1.02 (0.58 to 1.81) |
| Acute MI and acute cerebral stroke | Riise et al. 2019 | GH in 1st pregnancy | 134 | HR | 2.4 (1.1-5.5) | 1.8 (0.8-4.1) |
| Other circulatory disease † | Wilson et al. 2003 | GH in 1st pregnancy | 172 | IRR | NG | 1.51 (1.06-2.14) |
| Myocardial Infarction | Wilson et al. 2003 | GH in 1st pregnancy | 30 | OR | NG | 0.73 (0.32-1.63) |
| | Männistö et al. 2013 | A history of GH | 471 | IRR | NG | 1.75 (1.40-2.19) |
| | Schmiegelow et al. 2014 | A history of GH | 68 | HR | NG | 1.41 (0.19-10.21) |
| Intracerebral haemorrhage | Lin et al. 2016 | A history of GH | 27 | IRR | NG | 3.72 (3.63-3.81) |
| Ischaemic Stroke | Männistö et al. 2013 | A history of GH | 384 | IRR | NG | 1.59 (1.24-2.04) |
| | Schmiegelow et al. 2014 | A history of GH | 175 | HR | NG | 2.78 (1.13-6.82) |
| Cardiomyopathy | Behrens et al. 2016 | A history of GH | 1,448 | HR | NG | 1.83 (1.20-2.63) |
| Thromboembolic event | Kestenbaum et al. 2003 | A history of GH | 127 | HR | 1.4 (0.8-2.4) | 1.5 (0.9-2.5) |
| Cardiovascular Disease | Riise et al. 2018 | Pregnancies with GH in women with 2+ pregnancies | 19,869 | HR | NG | GH 1st pregnancy: 1.7 (1.5-2.0) |
| | | | | | | GH 2nd pregnancy: 2.4 (2.1-2.8) |
| | | | | | | 2+ GH pregnancies: 1.9 (1.8-2.0) |
| Coronary Heart Disease | Wikstrom et al. 2005 | Pregnancies with GH in women with 2+ pregnancies | 1,242 | IRR | GH 1st pregnancy: 1.9 (1.5-2.4) |
| | | | | | | GH 2nd pregnancy: 2.7 (2.0-3.5) |
| | | | | | | 2+ GH pregnancies: 3.3 (2.4-4.5) |

GH – gestational hypertension; MI – myocardial infarction; NG – not given; HR – Hazard Ratio, OR – Odds Ratio, IRR – incident rate ratio
* See Table S4 for adjustment. † Other circulatory disease excluding hypertension, cerebrovascular disease or coronary heart disease
### Table S9. Sensitivity Analyses of Risk of Cardiovascular Events Estimated from the Adjusted Meta-Analyses.

| Outcome                | Exposure                          | Sensitivity Analysis                      | Excluded Studies           | RR (95% CI)       | I² (95% CI) |
|------------------------|-----------------------------------|------------------------------------------|-----------------------------|-------------------|-------------|
|                        | GH in 1st pregnancy               | Excluding study(s) with the largest effect | Grandi 2017¹⁴               | 1.35 (1.08-1.69)  | 92% (86-96%) |
|                        |                                   | Fixed effects model                       | n/a                         | 1.52 (1.44-1.61)  | 92% (87-96%) |
| Coronary Heart Disease | GH in 1st pregnancy               | Excluding study(s) with the largest effect | Kestenbaum 2003¹⁵; Schmiegelow 2014¹⁶ | 1.65 (1.28-2.11) | 76% (46-89%) |
|                        |                                   | Fixed effects model                       | n/a                         | 1.39 (1.29-1.49)  | 85% (70-93%) |
|                        | A history of GH                   | Excluding study(s) with the largest effect | Kestenbaum 2003¹⁵; Schmiegelow 2014¹⁶ | 1.65 (1.28-2.11) | 76% (46-89%) |
|                        |                                   | Fixed effects model                       | n/a                         | 1.39 (1.29-1.49)  | 85% (70-93%) |
|                        | Coronary Heart Disease             | GH in 1st pregnancy                      | Excluding study(s) with the largest effect | 1.40 (1.17-1.66) | 73% (10-92%) |
|                        |                                   | Fixed effects model                       | n/a                         | 1.35 (1.25-1.45)  | 74% (27-91%) |
|                        | A history of GH                   | Excluding study(s) with the largest effect | Tooher et al. 2017¹³        | 1.49 (1.18-1.89)  | 78% (31-93%) |
|                        |                                   | Fixed effects model                       | n/a                         | 1.39 (1.28-1.52)  | 88% (72-95%) |
| Stroke                 | GH in 1st pregnancy               | Excluding study(s) with the largest effect | Not conducted *             | -                 | -           |
|                        |                                   | Fixed effects model                       | n/a                         | 1.19 (1.06-1.32)  | 82% (44-94%) |
|                        | A history of GH                   | Excluding study(s) with the largest effect | Not conducted *             | -                 | -           |
|                        |                                   | Fixed effects model                       | n/a                         | 1.33 (1.17-1.51)  | 70% (0-91%)  |
| Heart Failure          | A history of GH                   | Excluding study(s) with the largest effect | Not conducted *             | -                 | -           |
|                        |                                   | Fixed effects model                       | n/a                         | 1.75 (1.57-1.95)  | 63% (0-90%)  |

CI – Confidence Intervals; GH – Gestational Hypertension; RR – Relative Risk

* Fewer than four studies included in meta-analysis, so sensitivity analysis was not conducted
Table S10. Stratified Analyses of the Risk of Cardiovascular Disease Estimated from the Adjusted Meta-analyses.

| Exposure                      | Strata                        | Studies (N) | RR    | (95% CI) | $I^2$ | (95% CI) | P-value |
|-------------------------------|-------------------------------|-------------|-------|----------|-------|----------|---------|
| GH in 1st pregnancy           | Level of Adjustment           | Adequately/Well | 5     | 1.38    | 91%   | (83-96%) | 0.796   |
|                               | Poor                          | 2           | 1.60  | (1.50-1.72) | 82%  | (53-93%) |         |
|                               | Risk of Bias                  | Low Risk    | 5     | 1.51    | 93%   | (87-96%) | 0.904*  |
|                               | Not Low Risk                  | 2           | 1.75  | (1.43-2.14) | 94%  | (82-98%) |         |
|                               | Average follow-up             | <20 years   | 4     | 1.63    | 93%   | (86-96%) | 0.281   |
|                               | >20 years                     | 3           | 1.21  | (1.08-1.36) | 63%  | (0-92%)  |         |
|                               | Year of Publication           | Up to 2010  | 3     | 1.50    | 80%   | (35-94%) | 0.781   |
|                               | 2010 onwards                  | 4           | 1.53  | (1.44-1.62) | 96%  | (92-98%) |         |
|                               | Population                    | European    | 5     | 1.61    | 91%   | (81-95%) | 0.694*  |
|                               | Non-European                  | 2           | 1.20  | (1.06-1.36) | 95%  | (83-98%) |         |
| A history of GH               | Level of Adjustment           | Adequately/Well | 3     | 1.34    | 87%   | (64-96%) | 0.417   |
|                               | Poor                          | 4           | 1.41  | (1.21-1.65) | 82%  | (53-93%) |         |
|                               | Risk of Bias                  | Low Risk    | 4     | 1.31    | 66%   | (1-88%)  | 0.656*  |
|                               | Not Low Risk                  | 4           | 1.50  | (1.29-1.74) | 91%  | (76-96%) |         |
|                               | Average follow-up             | <20 years   | 3     | 2.40    | 0%    | (0-90%)  | 0.475   |
|                               | >20 years                     | 5           | 1.31  | (1.22-1.42) | 83%  | (57-93%) |         |
|                               | Year of Publication           | Up to 2010  | 3     | 1.28    | 89%   | (56-97%) | 0.863   |
|                               | 2010 onwards                  | 5           | 1.37  | (1.27-1.48) | 83%  | (61-93%) |         |
|                               | Population                    | European    | 3     | 1.27    | 70%   | (0-91%)  | 0.303*  |
|                               | Non-European                  | 5           | 1.90  | (1.58-2.28) | 72%  | (20-90%) |         |

CI – Confidence Intervals; GH – Gestational Hypertension; RR – Relative Risk; N - Number
* Test for interaction, all other – values are test for trend from meta-regression
Figure S1. Association between gestational hypertension in a woman’s first pregnancy and subsequent risk of cardiovascular events in unadjusted analyses.

| Author, year of publication | Events/Participants (N) | RR (95% CI) |
|-----------------------------|-------------------------|-------------|
| Cardiovascular Disease      |                         |             |
| Luoto 2009                  | 38/4,000                | 0.87 (0.61, 1.25) |
| Cair 2016                   | 178/302,686             | 1.18 (1.01, 1.37) |
| Bhattacharya 2012           | 1,365/32,828            | 1.19 (1.06, 1.34) |
| Lykke 2009                  | 1,194/748,461           | 1.68 (1.43, 1.98) |
| Riise 2018                  | 15,716/490,648          | 1.80 (1.66, 1.95) |
| Grandi 2017                 | 920/146,000             | 2.40 (1.88, 3.07) |
| Subtotal                    |                         | 1.46 (1.16, 1.83) |

| Coronary Heart Disease      |                         |             |
| Bhattacharya 2012           | 2,538/32,828            | 1.09 (1.00, 1.19) |
| Lykke 2009                  | 7,865/748,461           | 1.67 (1.41, 1.97) |
| Wikstrom 2005               | 2,579/403,550           | 2.00 (1.65, 2.43) |
| Riise 2018                  | 1,928/490,648           | 1.70 (1.31, 2.21) |
| Subtotal                    |                         | 1.56 (1.13, 2.16) |

| Stroke                      |                         |             |
| Bhattacharya 2012           | 1,365/32,828            | 0.97 (0.86, 1.09) |
| Riise 2018                  | 1,869/490,648           | 1.30 (0.95, 1.79) |
| Lykke 2009                  | 8,387/748,461           | 1.68 (1.43, 1.98) |
| Subtotal                    |                         | 1.28 (0.86, 1.90) |

CI – Confidence intervals; RR – Relative Risk
Figure S2. Association between a history of one or more pregnancies affected by gestational hypertension and subsequent risk of cardiovascular events in unadjusted analyses.

| Author, year of publication | Events/Participants | RR (95% CI) |
|-----------------------------|--------------------|-------------|
| Cardiovascular Disease      |                    |             |
| Luoto 2008                  | 98/4,000           | 1.18 (0.99, 1.40) |
| Cinillo 2015                | 9,000/13,640       | 1.19 (0.89, 1.59) |
| Andolf 2017                 | 18,191/278,591     | 1.34 (1.23, 1.45) |
| Kestenbaum 2003             | 83/103,589         | 2.90 (1.76, 4.78) |
| Subtotal [I-squared=74% (29-91%), p=0.008] |               | 1.37 (1.12, 1.69) |

CI – Confidence intervals; RR – Relative Risk
Figure S3. Association between a history of one or more pregnancies affected by gestational hypertension and subsequent risk of any stroke event in adjusted analyses.

| Author, year of publication | Events/Participants (N) | RR (95% CI) |
|-----------------------------|------------------------|-------------|
| Tooher 2017                  | NG/27,887              | 0.57 (0.14, 2.32) |
| Andolf 2017                 | 7,426/278,591          | 1.30 (1.14, 1.48) |
| Mannisto 2013               | 384/7,543              | 1.59 (1.24, 2.04) |
| Schmiegelow 2014            | 175/273,101            | 2.78 (1.13, 6.83) |
| Theilen 2016                | NG/152034              | 2.97 (1.49, 5.92) |
| Lin 2016                    | 27/36,950              | 3.72 (3.63, 3.81) |
| Overall                     | [I²=98% (97-99%); p<0.001] | 1.96 (1.06, 3.63) |

CI – Confidence intervals; NG – not given; RR – Relative Risk
Figure S4. Funnel plot of the studies contributing to the meta-analysis of the risk of cardiovascular disease after gestational hypertension in the first pregnancy.

Egger’s test p-value: 0.682. Vertical dashed lines indicate the confidence intervals from the pooled analysis. RR- Relative Risk
Figure S5. Funnel plot of the studies contributing to the meta-analysis of cardiovascular disease risk after a history of one or more pregnancies affected by gestational hypertension.

Egger’s test p-value: 0.051. Trim-and-fill estimate: RR=1.26 (1.15-1.39). Vertical dashed lines indicate the confidence intervals from the pooled analysis. RR: Relative Risk
Figure S6. Funnel plot of the studies contributing to the meta-analysis the risk of any stroke event after a history of one or more pregnancies affected by gestational hypertension.

Egger's test p-value: 0.382. Vertical dashed lines indicate the confidence intervals from the pooled analysis. RR- Relative Risk