Future cardiovascular disease risk for women with gestational hypertension: a systematic review and meta-analysis

**First authors’ surname:** Lo.

**Short title:** Gestational hypertension and CVD: a review

**Authors**:

Charmaine Chu Wen Lo\*1,2 BMedSc(Hons), BMed, Andre C Q Lo\*3, Shu Hui Leow3, Grace Fisher4, Beth Corker3, BSc, Olivia Batho3, Bethan Morris3, Monika Chowaniec3, Catherine J. Vladutiu5 PhD, Abigail Fraser6 PhD, Clare Oliver-Williams3,7 PhD

\* denotes equal contribution

**Correspondence**: Clare Oliver-Willliams. Cardiovascular Epidemiology Unit, Department of Public Health and Primary Care, University of Cambridge, Cambridge, United Kingdom. Email: [cto21@medschl.cam.ac.uk](mailto:cto21@medschl.cam.ac.uk) Tel: +44 (0) 1223 748653

**Affiliations**:

1. Faculty of Health and Medicine, University of Newcastle, Newcastle, New South Wales, Australia.

2. Liverpool Hospital, Liverpool, New South Wales, Australia

3. Homerton College, University of Cambridge, Cambridge, United Kingdom

4. Hills Road Sixth Form College, Hills Road, Cambridge, United Kingdom

5. Department of Obstetrics & Gynecology, School of Medicine, University of North Carolina, Chapel Hill, North Carolina

6. Population Health Sciences, Bristol Medical School, University of Bristol, Oakfield House, Oakfield Grove, Bristol BS8 2BN.

7. Cardiovascular Epidemiology Unit, Department of Public Health and Primary Care, University of Cambridge, Cambridge, United Kingdom.

**Subject Terms**: Women, Risk Factors, Pregnancy, Epidemiology, Hypertension, Meta-analysis

**Abstract**

**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 of cardiovascular events associated with gestational hypertension were extracted from the eligible studies. Where appropriate, estimates were pooled with inverse variance weighted random-effects meta-analysis.

Twenty-one studies involving 3,601,192 women (127,913 with gestational hypertension) were identified. Gestational hypertension in the first pregnancy was associated with an increased risk of overall cardiovascular disease (relative risk 1.45, 95% confidence interval, 1.17-1.80), and coronary heart disease (1.46, 1.23-1.73), but not stroke (1.26, 0.96-1.65) or thromboembolic events (0.88, 0.73-1.07). Women with one or more pregnancies affected by gestational hypertension were at greater risk of cardiovascular disease (1.81, 1.42-2.31), coronary heart disease (1.83, 1.33-2.51) and heart failure (1.77, 1.47-2.13), but not stroke (1.50, 0.75-2.99).

**Conclusions**

Gestational hypertension is associated with an increased 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.

**Study registration**

PROSPERO registration number: CRD42018119031.

**Key Words:** Pregnancy, Gestational Hypertension, Cardiovascular Disease, Women, Review

**Clinical Perspective**

**What Is New?**

In a systematic review of over 3 million women, we found that gestational hypertension is associated with an increased risk of cardiovascular disease, coronary heart disease and heart failure.

Non-significant trends towards an increased risk of stroke after gestational hypertension were found.

**What Are the Clinical Implications?**

Women with a pregnancy complicated by gestational hypertension are at increased risk of developing several different kinds of cardiovascular disease.

Women who experience gestational hypertension may benefit from counselling during and/or after pregnancy about their long-term cardiovascular risk.

**Introduction**

Gestational hypertension (GH), also known as pregnancy-induced hypertension, is defined as the onset of high blood pressure (at least 140 mmHg systolic or 90 mmHg diastolic) without proteinuria, on two occasions at least 4 hours apart, in an ordinarily normotensive pregnant woman after 20 weeks of gestation1,2. Rates of GH vary between countries, with 1-6% of pregnancies complicated by GH in Western countries3,4.

Pregnancy-induced hypertension is increasingly recognised as a risk factor for subsequent cardiovascular disease (CVD) in women5. In particular, pre-eclampsia, characterised by GH with proteinuria, is associated with a marked increase in CVD risk6–8 and has been incorporated in the American Heart Association guidelines for assessment of CVD risk in women9. It is unclear if GH and pre-eclampsia are manifestations of different severities of the same pathophysiological mechanism or represent separate pathologies10. Therefore, the increased 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 increased risk11–13 to more than twice the risk of some cardiovascular events13–18. 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 United Kingdom’s National Institute for Health and Care Excellence (NICE)19. 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 one 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 (MOOSE)20 and Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)21 protocols (eTables 1, 2). 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)22. 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 gestational hypertension and any cardiovascular outcome was of interest, including (1) overall CVD, (2) coronary heart disease (CHD), (3) any stroke, including ischaemic and haemorrhagic stroke, (4) heart failure, and (5) thromboembolic events. The details of the search terms are provided in eTable 3. 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, articles had to compare the risk of at least one cardiovascular outcome for women with previous GH, to that of women who had one 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 post-partum to minimise the risk of co-morbidity. Papers only evaluating pre-eclampsia, or combining both pre-eclampsia and gestational hypertension as an exposure, were excluded to minimise heterogeneity in the exposure. Study designs were limited to cohort studies and case-control studies. Exclusion criteria were: (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 gestational hypertension as an independent exposure.

**Selection of Studies and Data Extraction**

Using the software Abstrackr23, each abstract found with our search strategy were screened by two authors (CCWL, ACQL, SHL, GF, BC, OB, BM, MC). Any differences between reviewers were discussed and resolved by a third individual (CO). For relevant abstracts, full-texts were accessed to determine their eligibility for the review. Where two 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% confidence intervals (CI) 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 categorised 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 three of these four categories, and poorly adjusted studies controlled for variables in two or fewer categories.

Two authors independently evaluated the bias within each individual study using the validated Newcastle-Ottawa Scale, a semi-quantitative scale designed to evaluate the quality of non-randomised studies24. It allocates a maximum of nine 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 two 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 one or more pregnancies affected by GH, or only having normotensive pregnancies. Due to the distinction between these two classifications, our meta-analyses were conducted assessing risk associated with two exposures: 1) a diagnosis of GH in the first pregnancy, and 2) a history of one or more pregnancies affected by GH.

In order for a meta-analysis to be conducted, it was necessary to identify a minimum of three studies evaluating the risk of a particular cardiovascular outcome (e.g. stroke, CHD) associated with one of these exposures. If fewer than three 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 estimates for subgroups (e.g. 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 relative risks before combining these results with those from other studies.

When pooling results from separate studies, the inverse variance weighted method was used to combine odds ratios (OR), relative risk (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 χ2 statistic and the I2 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 following equation was used, ARI = (RR-1) x (ACR), where RR is the relative risk from the meta-analysis, and ACR is the assumed control risk.

Female-specific European Heart Network statistics for 2015 were used to estimate the ACR (i.e. the incidence) of overall CVD and CHD since the largest number of studies came from Europe25. Absolute risk increases 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 due to the non-significant 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 re-ran 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 studies26. 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 haemorrhage 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.

Five 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 since 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's tests for meta-analyses including six or more studies27. Upon evidence of funnel plot asymmetry and indication of significant bias from the Egger’s test, the trim-and-fill method was used to correct for funnel plot asymmetry28.

All tests were two-tailed and p-values of <0.05 were considered statistically significant. STATA software package (v14.2, STATA, College Station, Texas, USA) was used for all statistical analyses.

**Results**

Our search strategy identified 5,474 studies, of which 5,393 were excluded during the initial abstract screen. The remaining 81 articles were reviewed in full, resulting in 60 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 one or more pregnancies affected by gestational hypertension, from 18 cohort studies11-13,29–39 and 3 nested case-control studies15,18,40. Studies were conducted in Europe (12 studies11,12,14,16,29,30,33–35,37-39) and North America (5 studies 15,17,31,32,36), as well as in Taiwan (2 studies18,41) and Australia (1 study 13) (Table 1).

All of the studies ascertained GH and cardiovascular events through medical records, registry data or health insurance claims (Tables 1, eTable 4). The duration of follow-up varied from a median of 4.5 years16 to a maximum of 73 years17 (Table 1). Based on the Newcastle-Ottawa scale, five studies were judged to be at high risk of bias, and ten studies provided risk estimates that were poorly adjusted (eTables 5, 6).

**Gestational Hypertension in the First Pregnancy**

Eleven studies11,12,14,31,33,34,36–40, 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, eTables 7, 8). Of the nine 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 (35,876 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 studies11,12,14,31,34,36,37, RR=1.45, 95% CI: 1.17-1.80) and CHD (4 studies (11, 34, 37, 39), RR=1.46, 1.23-1.72), but not overall stroke (3 studies11,34,37, RR=1.26, 0.96-1.64) or thromboembolic events (3 studies11,34,40**,** RR=0.88, 0.73-1.07) (Figure 3). There was evidence of significant between-study heterogeneity for overall CVD (I2 = 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 unadjusted results were consistent with these findings (eFigure 1).

The absolute risk increases 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 three studies were not included in the meta-analyses (eTable 8). These studies evaluated heart failure, a composite outcome of MI and acute cerebral stroke, angina, MI, and other circulatory disease. Increased risks of heart failure and combined acute MI and acute cerebral stroke were noted, which both attenuated after adjustment (adjusted HR=1.37, 0.98-1.93 and adjusted HR=1.8, 0.8-4.1), respectively34,38. One study found no increased risk of MI (adjusted OR=0.73, 0.32-1.63), or angina (adjusted OR=1.02, 0.58-1.81), but noted an increased 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, 1.06-2.14)40.

**History of Gestational Hypertension**

Eleven studies from ten populations12,13,15–17,29,30,32,35,41, assessed risk of a cardiovascular outcome associated with a history of one 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 haemorrhage, ischaemic stroke, MI, and thromboembolic events (Figure 1, eTables 7, 8). Of the included studies, nine 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 an increased risk of overall CVD (8 studies13,15–18,29,32, RR=1.81, 1.42-2.32), CHD (4 studies13,17,29,35, 1.83, 1.33-2.51) and heart failure (3 studies13,17,29, RR=1.77, 1.47-2.13), but not overall stroke (3 studies29,30,35, RR=1.50, 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). An increased CVD risk was also observed in the meta-analysis of unadjusted findings (eFigure 2).

The absolute risk increases 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 seven studies were not included in the meta-analysis (eTable 8). These studies evaluated the risk of MI, intracerebral haemorrhage, ischaemic stroke, cardiomyopathy and thromboembolic events. Evidence of increased risks were found for cardiomyopathy (HR=1.83, 1.20-2.63), intracerebral haemorrhage (IRR=3.62, 3.63-3.81) and, in two studies, ischaemic stroke (IRR=1.59, 1.24-2.04, HR = 2.78, 1.13-6.82)16,30,35,41. A history of GH was also associated with MI in one study (IRR=1.75, 1.40–2.19)35, but not in a second study (HR=1.41, 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, 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 two pregnancies who were categorised 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. An increased risk of overall CVD relative to normotensive women was found for women with GH in their first pregnancy (HR = 1.7, 1.5-2.0), their second pregnancy (HR = 2.4, 2.1-2.8) and in both pregnancies (HR=1.9, 1.8-2.0)37. An increased CHD risk was also noted for women with GH in either their first pregnancy (IRR=1.9, 1.5-2.4), or second pregnancy (IRR=2.4, 1.8-3.2) and for those with two or more affected pregnancies (IRR=2.8 (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 (eTable 9). When all stroke events, including overall stroke and stroke subtypes (intracerebral haemorrhage and ischemic stroke), were included in the history of GH meta-analysis, there was evidence for an increased risk of any stroke outcome for women with one or more pregnancies affected by GH: 1.96 (1.06-3.63). Evidence for between-study heterogeneity was found in this analysis (98%, p<0.001) (eFigure 3).

The overall CVD analyses were separately stratified by average duration of follow-up, risk of bias, level of adjustment, year of publication and population (eTable 10). 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’s test: p = 0.935) (eFigure 4). 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 (eFigure 5). Use of the trim-and-fill method resulted in a relative risk 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) (eFigure 6).

**Discussion**

This systematic review found that women previously diagnosed with GH had an increased risk of overall CVD, CHD and heart failure, and some indication of an increased 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 GH42, however they focused on morbidity from CVD and cerebrovascular disease only. Our findings substantially builds upon it providing a comprehensive, holistic review of the risk of fatal and non-fatal cardiovascular events after GH.

This study adds to the growing literature on the relationship between women’s obstetric history and their subsequent risk of cardiovascular events. These include an increased risk of overall CVD with recurrent miscarriages43, preterm birth44, fetal growth restriction45 and pre-eclampsia46. The magnitude of association for overall CVD risk found in the current review is similar to that found with recurrent miscarriages43, preterm birth44 and fetal growth restriction45. Although the overall CVD risk associated with pre-eclampsia is greater than that of GH46.

**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. Due to the larger number of studies included in the overall CVD analysis, it was possible to assess the impact of study characteristics 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. It was possible that despite searching multiple databases without language or time restrictions, relevant studies were missed. Secondly, 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.

Thirdly, high heterogeneity (I2>70%) was found for most meta-analyses. This may be due to differences in study design, methodology, and 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 CVD40,47, 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 due to the inclusion of different International Classification of Diseases (ICD) codes to define the same outcome (eTable 4). Although all studies used robust measurement 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 in order to rule out chronic hypertension, the criteria for which has changed over time, notably in the United States48.

Fourthly, 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. Fifthly, 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 (eFigure 4). 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 generalisability of these findings to other populations.

**Implications for clinical practice**

Several theories have been proposed to explain the link between GH and 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, pre-pregnancy BMI is particularly important for GH risk49 and BMI, in general, is linked CVD development50,51. 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 health52. 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 women53.

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 complications54,55. There is evidence that lifestyle changes can be effective in mitigating maternal and fetal risks56, and research is underway to identify the ideal interventions57. Women who experience GH may also benefit from counselling during and/or after pregnancy about their long-term cardiovascular risk. Strategies that could be implemented after pregnancy may include discussion of heart age calculations58,59, 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 recognised in guidelines for assessing CVD risk in women9, 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, while many cardiovascular events have been entirely overlooked, such as peripheral arterial disease and transient ischemic attack. Furthermore, only two studies were identified that assessed a dose-response relationship, i.e. 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 increases with the number of affected pregnancies60,61, the limited evaluation of a dose-response relationship for GH needs addressing.

**Conclusion**

In conclusion, we found that GH is associated with an increased risk of overall CVD, specifically CHD and heart failure. The relative risk increase 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 increased risk and may benefit from prenatal and postnatal counselling to increase their awareness of strategies that can reduce their CVD risk during and after birth.

**Non-standard Abbreviations and Acronyms:**

ARI - absolute risk increases

ACR - assumed control risk

CVD - cardiovascular disease

CI - confidence intervals

CHD - coronary heart disease

DBP – diastolic blood pressure

DVT – deep vein thrombosis

GH - Gestational hypertension

HR - hazard ratios

IRR - incident rate ratio

ICD - International Classification of Diseases

MOOSE - Meta-Analysis of Observational Studies in Epidemiology

MI - myocardial infarction

NICE - National Institute for Health and Care Excellence

NHS – national health service

NG – not given

OR - odds ratios

PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-analyses

RR - relative risk

UK – United Kingdom

US – United States

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**Data Availability Statement:** All data generated or analyzed during this study are included in this published article and its supplementary information files.

**Supplemental Material:** eTables 1-10, eFigures 1-5, References 11-18, 29-41

**Affiliations:**

Charmaine Chu Wen Lo: Faculty of Health and Medicine, University of Newcastle, Newcastle, New South Wales, Australia. Liverpool Hospital, Liverpool, New South Wales, Australia

Andre C Q Lo: Homerton College, University of Cambridge, Cambridge, United Kingdom

Shu Hui Leow: Homerton College, University of Cambridge, Cambridge, United Kingdom

Grace Fisher: Hills Road Sixth Form College, Hills Road, Cambridge, United Kingdom

Beth Corker: Homerton College, University of Cambridge, Cambridge, United Kingdom

Olivia Batho: Homerton College, University of Cambridge, Cambridge, United Kingdom

Bethan Morris: Homerton College, University of Cambridge, Cambridge, United Kingdom

Monika Chowaniec: Homerton College, University of Cambridge, Cambridge, United Kingdom

Catherine J. Vladutiu: Department of Obstetrics & Gynecology, School of Medicine, University of North Carolina, Chapel Hill, North Carolina

Abigail Fraser: Population Health Sciences, Bristol Medical School, University of Bristol, Oakfield House, Oakfield Grove, Bristol BS8 2BN.

Clare Oliver-Williams: Homerton College, University of Cambridge, Cambridge, United Kingdom. Cardiovascular Epidemiology Unit, Department of Public Health and Primary Care, University of Cambridge, Cambridge, United Kingdom.

**Contributors**: CCWL and ACQL share joint first authorship. CACQL, SHL, GC, BC, OB, BM, MC, CJV, AF and CO were involved in designing the study. ACQL, SHL, GF, BC, OB, BM, MC and CO were involved in searching the database. CCWL, ACQL, SHL, GF, BC, OB, BM, and MC screened citations for inclusion. CCWL, ACQL, SHL and CO were involved in risk of bias analysis. CCWL, ACQL and CO were involved in extracting data and interpretation. CO analysed the data. CCWL, ACQL, CJV, AF and CO drafted the manuscript.

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**Figures Legends**

Figure 1: Identification of studies included in the review of gestational hypertension and risk of cardiovascular events.

*GH – gestational hypertension*

Figure 2: Association between gestational hypertension and cardiovascular events, showing summary relative risks for the meta-analyses of each outcome.

*CI – Confidence intervals; RR – Relative Risk*

Figure 3: Association between gestational hypertension in a woman’s first pregnancy and subsequent risk of cardiovascular events in adjusted analyses

*CI – Confidence intervals; RR – Relative Risk*

Figure 4: Association between a history of one or more pregnancies affected by gestational hypertension and subsequent risk of cardiovascular events in adjusted analyses

*CI – Confidence intervals; NG – not given; RR – Relative Risk*

**Tables**

# Table 1: Characteristics of Studies Included in the Review

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| First author, year | Details of Cohort | Study design | N of women | N of women with GH | GH definition | Method of GH Ascertainment | Duration of Follow Up (Years) | Age at enrolment (Years) | Outcome(s) | Method of Outcome Ascertainment |
| Andolf et al. 201729 | Swedish National Register Study 1973-2009 | Cohort study | 283,990 | 4,762 | ICD codes | Medical Records | Mean: 35 | Mean: 26.19 | Heart Failure † | Medical records |
| Behrens et al. 201630 | Danish medical registries, 1978-2012 | Cohort study | 834,919 | 11,047 | ICD codes | Medical records | Mean: 17.9 | Median: 25-29 | Cardiomyopathy | Medical records |
| Bhattacharya et al. 201211 | Aberdeen Maternity and Neonatal Databank & NHS medical records, 1950-2008 | Cohort study | 32,828 | 8,891 | ICD codes | Medical records | Max: 58 | Mean: 24.27 | CVD, CHD, Stroke, Pulmonary embolism | Medical records |
| Cain et al 201631 | Florida maternal & infant databases, 1998-2009 | Cohort study | 302,686 | 17,150\* | ICD codes | Medical records | Median: 4.9 | Mean: 25.1 | CVD | Medical records |
| Cirillo et al. 201532 | US Child Health and Development Studies, 1959-2011 | Cohort study | 10,721 | 1,662 | ≥1 blood pressure reading of > 140/90 mmHg after 20 weeks gestation | Medical records | Range: 44-52 | Median: 26 | Fatal CVD | Death certificates |
| Grandi et al. 2017\*14 | UK Clinical Database, 1990-2013 | Cohort study | 146,000 | Not given | Read codes | Medical records | Median: 4.7 | Mean: 29.24 | CVD | Medical records |
| Kestenbaum et al. 200315 | Washington State Birth Events Record Database & Comprehensive Hospital Abstract Reporting System database, 1987-2001 | Nested Case Control | 103,589 | 10,687 | ICD codes | Birth certificate data | Mean 7.8 | Mean: 26.23 | CVD, Thromboembolic events | Medical records |
| Lin et al. 201641 | Taiwan national health insurance database, 2000-2013 | Cohort study | 36,950 | 7,390 | ICD codes | Health insurance claims data | Max: 13 | Mean: 31.06 | Intracerebral haemorrhage | Health insurance claims data |
| Luoto et al. 200812 | Women giving birth in Helsinki hospitals, 1954-2005 | Cohort study | 4,000 | 98 | Coding not specified | Medical records | Mean: 44 | NG | Fatal CVD | Medical records |
| Lykke et al. 200934 | Danish medical registries, 1978-2007 | Cohort study | 782,287 | 7,449 | ICD codes | Medical Records | Mean: 14.6 | Mean: 26.8 | CHD, Heart Failure, Thromboembolic event, Stroke | Medical records |
| Lykke et al. 201033 | Danish medical registries, 1978-2007 | Cohort study | 782,287 | 7,449 | ICD codes | Medical Records | Median: 14.8 | Mean: 26.8 | Fatal CVD | Medical records |
| Männistö et al. 201335 | Northern Finland Birth Cohort, 1966-2000 | Cohort study | 7,543 | 991 | SBP ≥145 mmHg and/or DBP ≥95 mmHg | Assessed during pregnancy as part of study | Mean: 39.4 | Mean: 26.76 | CHD, MI, Heart Failure, Stroke | Medical records |
| Ray et al. 200536 | Ontario Health Insurance Plan (OHIP), 1990-2004 | Cohort study | 963,263 | 20,942 | ICD codes | Health-care administrative databases | Median 8.7 | Mean: 28 | CVD | Hospital database |
| Riise et al. 201837 | Norweigian registries, 1980-2009 | Cohort study | 587,755 | 11,600 | SBP ≥140 mmHg, DBP ≥90 mmHg, or >15 mmHg BP increase  measured <20 weeks gestation | Medical records | Median: 14.3 | Mean: 26.3 | CVD, CHD, stroke | Medical records |
| Riise et al. 201938 | Norweigian registries, 1980-2009 | Cohort study | 20,075 | 364 | SBP ≥140 mmHg, DBP ≥90 mmHg, or >15 mmHg BP increase  measured <20 weeks gestation | Medical Records | Median: 11.4 | Mean: 26.0 | Composite: acute myocardial infarction (AMI) or acute cerebral stroke | Medical Records |
| Schmiegelow et al. 201416 | Danish registries, 2004-2009 | Cohort study | 273,101 | 2,903 | ICD codes | Medical records | Median: 4.5 | Median: 30.4 | MI, Ischaemic stroke, CVD | Medical records |
| Theilen et al. 201617 | 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. 201713 | Royal Prince Alfred Women and Babies hospital, Australia, 1980-2009 onwards, | Cohort study | 27,887 | 625 | ICD codes | Medical Records | Median: 20‡ | Mean: 27 | CVD, CHD, Stroke | Registry, discharge |
| Wikstrom et al. 200539 | Swedish Medical Birth Register, 1987-2001 | Cohort study | 391,017 | 7,936 | ICD codes | Medical records | Max: 15 | Range: 15-64 | CHD | Registry (Cause of Death, Hospital Discharge) |
| Wilson et al. 200340 | Aberdeen maternity and neonatal databank, 1951-1999 | Nested case-control | 2,394 | 1,197 | DBP ≥90mmHg twice at 4+ hours apart or 1 reading of ≥ 110mmHg | Medical records | Max: 48 | Mean: 24.2 | Angina, MI, DVT, Other circulatory disease (not hypertension, CHD or cerebrovascular disease) | Medical and death records |
| Yeh et al. 201418 | Taiwan National Health Insurance database, 1998-2009 | Nested case-control | 5,765 | 725 | ICD codes | Health insurance claims data | Median: 5.8 | Mean: 29.8 | CVD | Medical records |

CHD – coronary heart disease; CVD – cardiovascular disease; DBP – diastolic blood pressure, DVT – deep vein thrombosis; GH – gestational hypertension; ICD – International classification of diseases; MI – myocardial infarction; NHS – national health service; UK – United Kingdom; US – United States

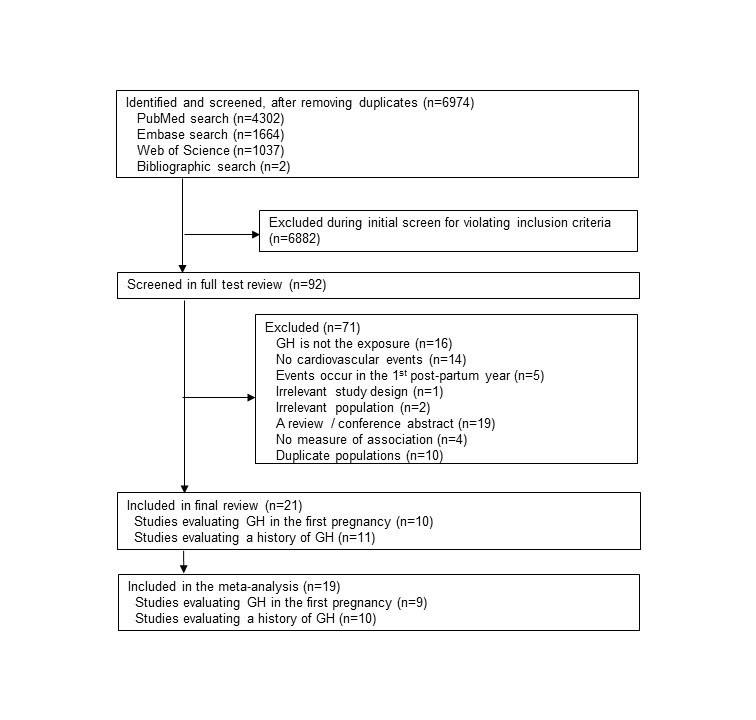
\* Cain et al. and Grandi et al did not indicate how many patients had GH, and the total number of women was estimated

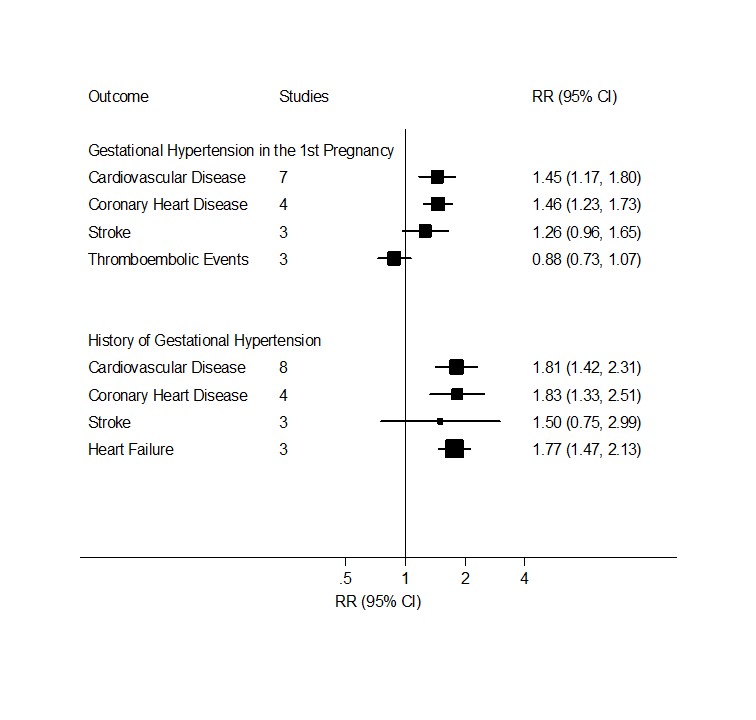
† Stroke, CHD and CVD also reported, but not included in meta-analysis as same population used in Lykke et al. 2009

‡ Median time from index pregnancy to onset of CVD – no follow-up duration given for full cohort

**Figures**

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