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# Family history of hypertension, cardiovascular disease or diabetes and risk of developing preeclampsia: A systematic review.

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**Declaration of Interest:** None

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**Abstract:**

Preeclampsia is a severe pregnancy complication with high potential for adverse effects on maternal and fetal health during the perinatal period. It is also associated with an increased risk of maternal cardiovascular disease later in life. Development of preeclampsia can be decreased by prescribing low-dose aspirin to high-risk women. At present, maternal and pregnancy factors are used to assess the risk of preeclampsia. One additional factor that could add to the assessment of risk is a family history of hypertension, cardiovascular disease, or diabetes, especially for

nulliparous women who do not have a pregnancy history to inform treatment decisions. Therefore, we conducted a systematic review to assess the association between family history of the aforementioned conditions and preeclampsia. Four databases including MEDLINE, EMBASE, the Cochrane Library, and CINAHL/pre-CINAHL were searched for observational studies that examined a family history of hypertension, cardiovascular disease, or diabetes in women with preeclampsia and in a control population. Studies were evaluated for quality using the Newcastle-Ottawa Scale. A total of 84 relevant studies were identified. A meta-analysis was not conducted due to suspected heterogeneity in the included studies. Most studies reported a positive association between a family history of hypertension or cardiovascular disease and the development of preeclampsia. The majority of studies examining family history of diabetes reported non-significant associations. Overall, family history of hypertension or cardiovascular disease is associated with a higher risk for developing preeclampsia and should be considered when assessing women in the first trimester for low-dose aspirin.

**Résumé**

La pré-éclampsie est une grave complication de grossesse qui comporte un risque élevé d'effets défavorables sur la santé maternelle et fœtale en période périnatale. La pré-éclampsie est également associée à une augmentation du risque de maladies cardiovasculaires plus tard dans la vie chez la mère. Il est possible de réduire le risque de pré-éclampsie en prescrivant de l'aspirine à faible dose aux femmes à risque élevé. À l'heure actuelle, on a recours aux facteurs maternels et obstétricaux afin d'évaluer le risque de pré-éclampsie. Les antécédents familiaux d'hypertension, de maladies cardiovasculaires et de diabète, en particulier chez les femmes nullipares qui n'ont pas d'antécédents de grossesse pouvant orienter les décisions relatives au traitement, constituent un facteur supplémentaire dont on peut tenir compte lors de l'évaluation

du risque. Nous avons donc mené une revue systématique afin de déterminer la corrélation entre la pré-éclampsie et les antécédents familiaux de ces maladies. Des recherches ont été effectuées dans quatre bases de données, notamment Medline, Embase et Cochrane Library, ainsi que CINAHL/pré-CINAHL, pour trouver des études observationnelles ayant examiné les antécédents familiaux d'hypertension, de maladies cardiovasculaires et de diabète chez les femmes atteintes de pré-éclampsie et au sein d'une population témoin. On a évalué la qualité des études au moyen de l'échelle de Newcastle-Ottawa. Au total, 84 études pertinentes ont été répertoriées. Aucune méta-analyse n'a été menée en raison d'une hétérogénéité soupçonnée des études retenues. La plupart des études indiquent une association positive entre les antécédents familiaux d'hypertension ou de maladies cardiovasculaires et la manifestation d'une pré-éclampsie. La majorité des études ayant examiné les antécédents familiaux de diabète ont indiqué une association non significative. Dans l'ensemble, les antécédents familiaux d'hypertension et de maladies cardiovasculaires sont associés à une augmentation du risque de pré-éclampsie. Il y a donc lieu d'en tenir compte au premier trimestre au moment d'évaluer si on doit envisager un traitement préventif par aspirine à faible dose.

**Keywords:** Preeclampsia, Family History, Hypertension, Cardiovascular Disease, Diabetes, Risk Factor



**Introduction:**

Preeclampsia is a severe complication of human pregnancy affecting 3-5% of women worldwide [1,2]. Although preeclampsia has long been recognized, the pathophysiology is still poorly understood. At present, preeclampsia is understood to be a syndrome in which the

common outcome of hypertension, proteinuria and end organ damage is the result of many possible insults which can include preclinical cardiovascular disease [3]. In fact, there is a greater prevalence of cardiovascular disease later in life in women who had preeclampsia [4-6]. In this subset of women, risk factors for cardiovascular disease are likely present at the time of pregnancy and could be used to predict the development of preeclampsia.

Other than delivery, there are no interventions that cure preeclampsia once it develops. However, low-dose aspirin (LD-ASA)[*] started before 16 weeks of gestation has been shown to decrease the incidence of severe, early-onset preeclampsia, particularly in women at high risk [7-9]. The National Institute for Clinical Excellence (NICE), the Society of Obstetricians and Gynaecologists of Canada (SOGC) and the American College of Obstetricians and Gynecologists (ACOG) all recommend early initiation of LD-ASA for women at high risk of preeclampsia [10-12]. The current guidelines defining high-risk women differ between these institutions (Table 1). Determining which nulliparous woman receive a recommendation to take LD-ASA is difficult and based on a number of potential risk factors for PE. The SOGC alone includes family history of early-onset cardiovascular disease as a recommendation for referral to a specialist [11]. Other more prevalent non-modifiable risk factors including family history of hypertension or diabetes may also be associated with preeclampsia. Including these risk factors in an early pregnancy assessment may allow identification of high-risk women who would most benefit from LD-ASA. Therefore, a systematic review was undertaken to determine if a family history of cardiovascular disease, hypertension or diabetes should be included in the risk factors that suggest initiating women on LD-ASA.

[*] Abbreviations: American College of Obstetricians and Gynecologists (ACOG), low dose aspirin (LD-ASA), National Institute for Clinical Excellence (NICE), odds ratio (OR), relative risk (RR), Society of Obstetricians and Gynaecologists of Canada (SOGC)

**Methods:**

Four databases including MEDLINE, EMBASE, the Cochrane Library and CINAHL/pre-CINAHL were searched for relevant case-control and cohort studies. Search strategies were designed for each database after consultation with a librarian (Supplementary Table 1). A protocol was submitted to PROSPERO (ID: 177175, approval pending). There was no lower date limit on the search which was performed on March 8, 2020. Articles were included if they were in English and presented data assessing family history of hypertension, cardiovascular disease or diabetes in women with hypertensive diseases of pregnancy and a control group. Studies that determined family history in women who were more than one year postpartum were excluded as it could not be assumed that a positive family history was present before/during pregnancy. Articles examining family history of preeclampsia as a risk factor were not included as this risk factor is already well-studied and accepted as risk factor in all three of the SOGC, ACOG and NICE guidelines.

The online systematic review tool, covidence.org, was used to organize and assess the search results. Title and abstract reviews were completed concurrently by two independent reviewers to select publications for full text review. The same two independent reviewers completed the full text review and selected articles for data extraction. Abstract publications were included if they presented a measure of association or raw data allowing calculation of a measure of association. Emails were sent to the authors of studies that stated but did not report non-significant adjusted odds ratios to request this information. Data extraction was completed using a pre-formed template by two independent reviews. The study design, information on the criteria for cases and controls, and definition of family history was collected in addition to the

sample sizes and measures of association. Any factors used for matching or for multivariate analysis were also recorded.

Quality of the studies was assessed by two independent reviewers using the Newcastle-Ottawa Scale [13,14]. This tool details 9 parameters of cohort and case-control study design including cohort or case/control selection, assessment of the outcome/exposure assessment and comparability of the two groups. Additionally, studies were assessed for appropriate sample size and prevalence of exposure [15]. Each study was given a score out of 10. Scores greater than 8/10 were rated as high quality, scores from 6-7 were rated as moderate quality and scores of 5 or less were rated as low quality. Any conflicts between the two independent reviewers at any stage were resolved with discussion.

Included publications were grouped by the type of family history assessed (hypertension, cardiovascular disease, diabetes) and by the case definition used (chronic hypertension, gestational hypertension, preeclampsia, superimposed preeclampsia on chronic hypertension or any combination thereof). Studies that recruited women with known hypertension pre-pregnancy or before 20 weeks were determined to have been examining chronic hypertension. Studies that defined the outcome as new-onset hypertension with no other systemic effects occurring after 20 weeks were defined as examining gestational hypertension. Studies with the outcome of new-onset hypertension and additional systemic effects or proteinuria were defined as examining preeclampsia. Finally, studies that recruited women who had known hypertension with new systemic symptoms or worsening of their blood pressure after 20 weeks were defined as examining superimposed preeclampsia on chronic hypertension. Studies that used a broad or combination case definition were reported qualitatively. Studies that used a clear case definition of preeclampsia alone were graphed for analysis. R and RStudio were used to plot the crude and

adjusted odds ratios (ORs) in forest plots. Studies that presented relative risks (RRs) were excluded from these plots. A meta-analysis was not performed on the study results because of heterogeneity in the study case definitions, study populations and factors used for adjustment.

**Results:**

The initial searches returned 20351 studies. 4098 studies were removed as duplicates leaving 16253 studies for title/abstract review. After excluding 15977 studies based on the title/abstract, 276 studies were included for full text review. At this stage, 167 studies were excluded as irrelevant, not in English, duplicates or for not reporting measures of association or raw data that allowed a measure of association to be calculated. The full texts of 18 studies were inaccessible. Overall, 91 studies were included for data extraction. Two additional studies had been previously identified and were included at this stage for a total of 93 studies. During data extraction, 9 studies that reported on the same population of participants as other studies by the same authors were excluded. In these cases, the most appropriate study of the set was included based on reporting of multivariate rather than univariate analyses, appropriate definition of preeclampsia and larger sample sizes. Overall, 84 studies were included for analysis (Figure 1).



*Family history of hypertension:*

Seventy-three cohort and case-control studies presented data on the relationship between family history of hypertension and the risk of hypertensive disorders in pregnancy (Supplementary Table 2). Few studies defined family history of hypertension by including an age threshold, specifying first degree relative or confirming the diagnosis instead reporting on

"family history of hypertension" alone. Of the 9 studies that used the broadest definition of hypertensive disorders of pregnancy (including chronic hypertension, gestational hypertension, preeclampsia, or preeclampsia superimposed on chronic hypertension), 5 reported significant associations between family history of hypertension and development of a hypertensive disorder of pregnancy. Similarly, 4 of the 8 studies that did not differentiate between gestational hypertension and preeclampsia reported a significant association. Eight of the 11 studies that analyzed gestational hypertension separately showed an association with family history of hypertension. Of the 5 studies that restricted analysis to cases with preeclampsia and/or superimposed preeclampsia alone, the majority (4/5) reported a significant association.

When the included studies were narrowed to those that examined preeclampsia alone, 48 studies were appropriate for inclusion. Twenty-six showed a significant association between family history of hypertension and risk of preeclampsia while 20 were non-significant. One moderate-quality study reported a significant protective association between family history of hypertension and preeclampsia [16]. The studies that compared cases with preeclampsia to normotensive controls and presented crude (Figure 2A) or adjusted ORs (Figure 2B) were graphed in forest plots. Studies were excluded from this analysis if they presented a RR [17-21], included women with hypertension during pregnancy in the control group [22], or did not present a numerical OR despite stating that the adjusted OR was non-significant [23,24].

Only one study included an age limit for diagnosis of essential hypertension and reported a significant association between early-onset hypertension in a parent and development of preeclampsia [25]. When hypertension in a parent or a sibling was assessed, the risk of preeclampsia seemed to be higher with a family history of hypertension in a sibling [26-28]. Only four studies assessed a family history of hypertension in a mother or a father separately

[20,25,26,29]. Although no studies directly compared between hypertension in a mother/father, the two high quality studies reported similar OR/RRs for the risk of preeclampsia with maternal or paternal hypertension [25,26] suggesting that the risk association with family history of hypertension in a mother or in a father is similar. Rigo et al. reported a larger risk of preeclampsia associated with a family history of hypertension in both parents [25]. Likewise, when the number of relatives affected was quantified, having a family history of hypertension in two or more relatives was associated with a higher risk of preeclampsia than one relative alone [19]. Family history of hypertension in both a parent and a sibling was also associated with a higher risk of preeclampsia [27,28]. Overall, a family history of hypertension appears to increase the risk of preeclampsia. Hypertension in more than one relative or appearing at a younger age in relatives may suggest increased risk.

*Family history of cardiovascular disease*.

Fourteen studies examined the relationship between family history of cardiovascular disease, frequently defined as history of myocardial infarction, and development of preeclampsia (Supplementary Table 3). Two studies included a composite of either myocardial infarction or stroke in a family member [30,31]. Most, but not all studies, specified family history in a first degree relative.

Two studies examined hypertensive disorders of pregnancy in aggregate. One reported a significant association with family history of cardiovascular disease [32] while the other reported a significant association [30]. Two studies that examined gestational hypertension reported non-significant associations with family history of cardiovascular disease [19,33]. One study

examined cases with either preeclampsia or gestational hypertension and reported a significant protective association with family history of cardiovascular disease [34].

Of the 11 studies that examined preeclampsia alone, 6 reported a significant association between family history of cardiovascular disease and preeclampsia. The studies that compared cases with preeclampsia to normotensive controls and presented crude (Figure 3A) or adjusted ORs (Figure 3B) were graphed in forest plots. Two studies were excluded for presenting RRs [19,35] and one study was excluded as it did not report the adjusted OR despite stating that it was non-significant [24]. All three of these studies had reported non-significant associations between preeclampsia and family history of cardiovascular disease.

Three studies included age cut-offs for the diagnosis of early cardiovascular disease. Each study used a different age. One study reported a non-significant association [36] while the other two reported significant associations [25,32]. The majority of the studies assessed family history of cardiovascular disease in first degree relatives but only two studies examined specific family members. Both studies reported similar ORs for a history of hypertension in a mother or in a father [25,31]. Overall, the studies indicate an increased risk of preeclampsia with a family history of cardiovascular disease. The age cut-off for early cardiovascular disease and whether the mother or father was diagnosed did not affect the strength of association with development of preeclampsia.

*Family history of diabetes:*

Thirty studies examined family history of diabetes and risk of hypertensive disorders of pregnancy (Supplementary Table 4). In these studies, family history of diabetes was typically not

clearly defined. Few studies specified an age threshold, determined which family members were affected or confirmed the diagnosis.

Of the four studies using a broad definition of hypertensive disorders of pregnancy, 3reported non-significant associations between family history of diabetes and risk of hypertension in pregnancy. Two studies examined cases with either preeclampsia or gestational hypertension with one reporting a significant association and one reporting a non-significant association. Only one of two studies that examined gestational hypertension cases alone reported a significant association. Likewise, of the two studies that included women with preeclampsia or superimposed preeclampsia, one reported a significant association with family history of diabetes and the other did not.

There were 22 studies with a clear case definition of preeclampsia. Of these studies, 14 reported a non-significant association between family history of diabetes and preeclampsia while 8 reported a significant association. The studies that compared cases with preeclampsia to normotensive controls and presented crude (Figure 4A) or adjusted ORs (Figure 4B) were presented in forest plots. Three studies were excluded for presenting RRs [18,19,35] and three studies could not be plotted as they did not present the numerical adjusted ORs despite stating that they were non-significant [23,24,37]. All six of these studies had reported non-significant associations.

No studies specified age of onset as part of the criteria for family history of diabetes. One study examined family history of diabetes in specific family members. Family history of diabetes in a sibling was significantly associated with risk of preeclampsia but family history of diabetes in a mother or father was not [27]. A second study examined the number of affected relatives but found no association between family history of diabetes and risk of preeclampsia whether one, or

more than two relatives were affected [19]. Overall, the evidence for an association between family history of diabetes and increased risk of preeclampsia is not strong.

*Family history of hypertension/cardiovascular disease/diabetes composites:*

Three studies examined composites of family history of hypertension, cardiovascular disease or diabetes (Supplementary Table 5). One reported no association between family history of hypertension/diabetes and risk of gestational hypertension [38]. A second found a significant association between family history of hypertension, dyslipidemia, heart attack, stroke, angina or vascular surgery in a father and risk of preeclampsia or superimposed preeclampsia [39]. The third reported an increased risk of superimposed preeclampsia with a family history of hypertension or cardiovascular disease in a population of women with chronic hypertension [40]. Overall, examining a composite family history of hypertension and cardiovascular disease may be more useful as a risk factor than a composite including family history of diabetes, but the evidence is limited.

**Discussion:**

Numerous studies have examined the association between family history of hypertension, cardiovascular disease, or diabetes with the development of preeclampsia; most studies support such an association. However, the identified studies have limitations. Many of the studies used vague definitions of family history based solely on patient knowledge and recollection. Few studies specified which relatives were affected and at what age. Ideally, the research definition of family history would stipulate a confirmed diagnosis in a first degree relative (mother, father,

sibling). Recall bias may also be a concern as family history was typically assessed after diagnosis of preeclampsia. Although this late assessment in many studies likely misclassified some participants, it is ultimately more representative of clinical practice. A second limitation is that the definition of preeclampsia was heterogenous between the studies, likely due to changes in clinical practice over time. Most studies diagnosed preeclampsia as new-onset hypertension and proteinuria after 20 weeks gestation. Other studies used a more modern definition by including signs of end-organ damage in the diagnosis without requiring proteinuria. The inclusion of cases with HELLP syndrome and eclampsia was also variable between studies. Finally, several studies were limited by small numbers of cases and controls which may explain the large confidence intervals seen in some publications.

This systematic review also has limitations. Although a thorough search strategy was used and abstract publications were included, articles written in languages other than English were excluded. Furthermore, only articles with full-text available were included. There is also no guarantee that studies with negative results were published and thus accessible. Even within the published studies, reporting bias is possible. In general, family history was included in a multivariate analysis only if significant in the univariate analysis. Some studies additionally did not report the adjusted ORs if they were non-significant. In the case of family history of hypertension and family history of cardiovascular disease, the majority of studies support an association with risk of preeclampsia. However, in the case of family history of diabetes, the adjusted ORs available for comparison are mostly significant and may lead to misleading conclusions if the missing non-significant adjusted ORs and non-significant crude ORs are not considered. Conversely, one strength of this review lies in the exclusion of studies that ascertained family history years after the pregnancy. In these studies, the diagnosis of family

members may have occurred after the pregnancy and is therefore not appropriate to be considered as a possible risk factor for development of preeclampsia during pregnancy. Although not included in the review, several of these studies did report significant associations between family history of hypertension or cardiovascular disease and having a previous hypertensive disorder of pregnancy [41-43]. Overall, the evidence supports an association between family history of hypertension, family history of cardiovascular disease and risk of preeclampsia.

Family history may be a more important risk factor if present in a first degree relative, at a younger age or in a greater number of relatives. However, recent research indicates that assessment of premature cardiovascular disease versus any cardiovascular disease in the family does not refine the risk associated with a positive family history [44,45]. In fact, the age of diagnosis and which relative is affected may not be required in the definition of family history. More studies would be needed to determine if a greater number of affected relatives with family history of hypertension or cardiovascular disease is a stronger predictor of preeclampsia.

Using family history of hypertension or cardiovascular disease as an indicator of risk for preeclampsia has some inherent limitations. All three diseases are linked to age. Family history is more likely to be positive in women of advanced maternal age or in women who were born to mothers of advanced maternal age. However, most studies corrected for maternal age, suggesting that family history of hypertension or cardiovascular disease is an independent risk factor as well. Family history of these cardiovascular risk factors has the potential to capture environmental and genetic factors that predispose to both preeclampsia and later cardiovascular disease. In fact, the presence of family history of hypertension or cardiovascular disease could help stratify women who experienced preeclampsia into high-risk and low-risk categories for later cardiovascular disease and identify the need for postpartum risk screening, lifestyle

modification and possibly therapeutic intervention [4,46]. Overall, family history of hypertension or cardiovascular disease is associated with a higher risk of preeclampsia and should be considered when assessing women for LD-ASA therapy.

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**Table 1: ACOG, NICE and SOGC guidelines for determining risk of preeclampsia and need for aspirin treatment.**

| *ACOG 2018* | *NICE 2019* | *SOGC 2014* |
|---|---|---|
| Low dose aspirin started before 16 weeks for women with:<br>One of:<br>- history of preeclampsia<br>- multifetal gestation<br>- renal disease<br>- autoimmune disease<br>- type 1 or type 2 diabetes<br>- chronic hypertension<br><br>Or more than one of:<br>- first pregnancy<br>- maternal age >35 years<br>- body mass index >30<br>- family history of preeclampsia<br>- African American ethnicity<br>- low socioeconomic status<br>- low birthweight<br>- previous small-for-gestational age<br>- previous adverse pregnancy outcomes<br>- pregnancy interval >10 years | 75-150 mg aspirin started at 12 weeks for women with:<br>One of:<br>- previous hypertension in pregnancy<br>- chronic kidney disease<br>- autoimmune disease<br>- type 1 or type 2 diabetes<br>- chronic hypertension<br><br>Or more than one of:<br>- first pregnancy<br>- maternal age >40<br>- pregnancy interval >10 years<br>- body mass index >35<br>- family history of preeclampsia<br>- multifetal gestation | 75-162 mg aspirin and calcium before 16 weeks for women with:<br>One of:<br>- previous preeclampsia<br>- anti-phospholipid antibody syndrome<br>- pre-existing hypertension<br>- pre-existing renal disease<br>- pre-existing diabetes<br>- multiple pregnancy<br><br>Or specialist referral with two or more of:<br>- maternal age >40<br>- family history of preeclampsia<br>- family history of early cardiovascular disease<br>- lower maternal birthweight or preterm delivery<br>- heritable thrombophilias<br>- increased pre-pregnancy triglycerides<br>- non-smoking<br>- cocaine/methamphetamine use<br>- previous miscarriage <10 weeks<br>- overweight/obese<br>- first pregnancy<br>- new partner<br>- short duration of relationship<br>- reproductive technologies<br>- pregnancy interval >10 years |

| | | |
|---|---|---|
| | | - initial BP >130/80mmHg<br>- vaginal bleeding<br>- gestational trophoblastic disease<br>- abnormal PAPP-A or βHCG |

**Figure Legends:**

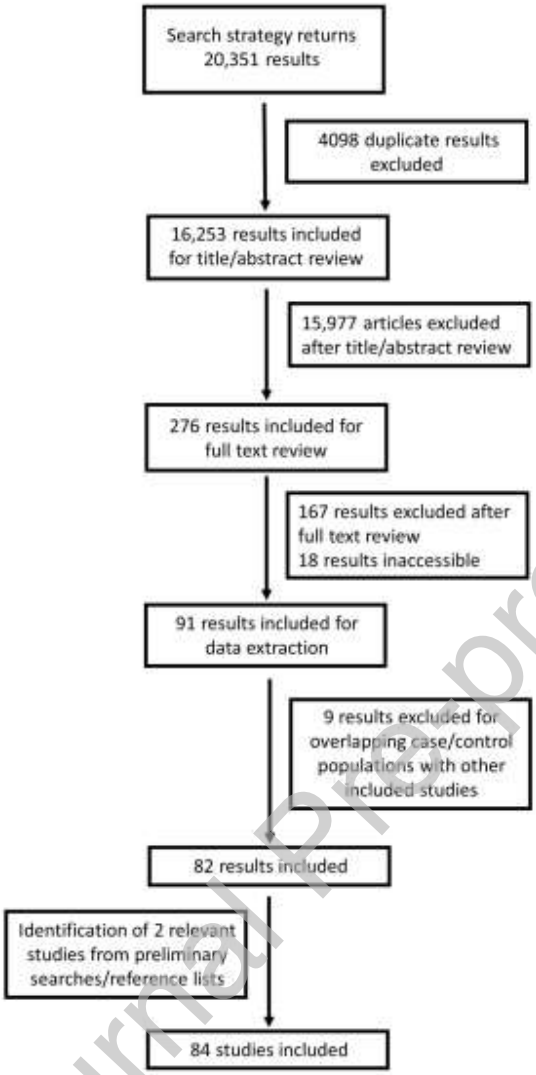




**Figure 1: Search Strategy.** A search was completed in the four selected databases with 20351 results. After review, 84 studies were included.

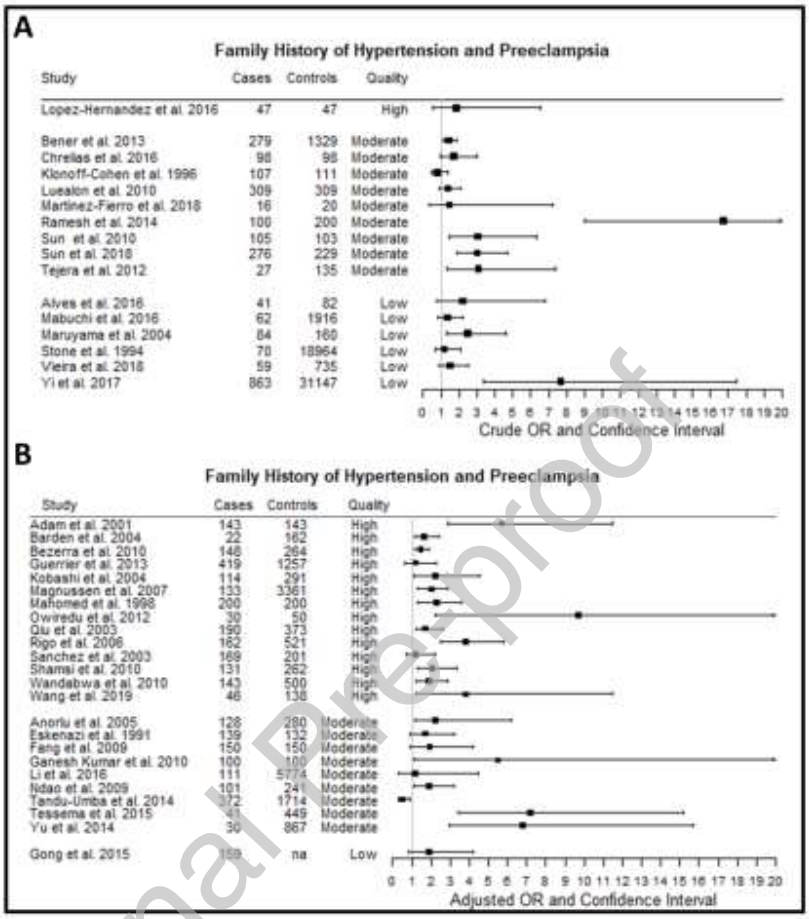




**Figure 2: Forest Plot of Studies Examining Family History of Hypertension.** Seventy-three studies examined the association between family history of hypertension and preeclampsia. The crude odds ratios (A) and adjusted odds ratios (B) with 95% confidence intervals from studies with a clear definition of preeclampsia and a normotensive control group are presented here. Five studies were excluded for presenting RRs. Two studies with non-significant adjusted ORs are not

presented as the numerical ORs were not available. Most studies reported a positive association between any family history of hypertension and preeclampsia.

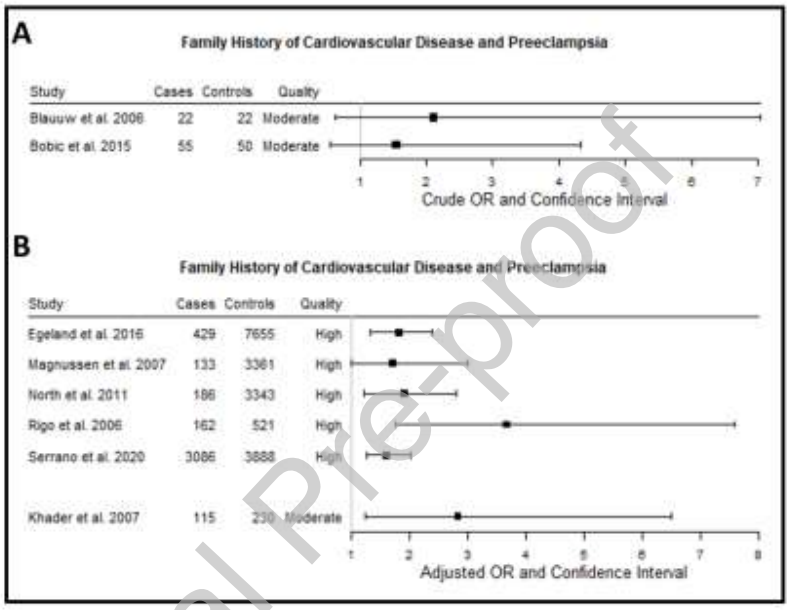


**Figure 3: Forest Plot of Studies Examining Family History of Cardiovascular Disease.** Fourteen studies examined the association between family history of cardiovascular disease and preeclampsia. The crude odds ratios (A) and adjusted odds ratios (B) with 95% confidence

intervals from studies with a clear definition of preeclampsia and a normotensive control group are presented here. Two studies were excluded for presenting RRs. One study with a non-significant adjusted OR was not presented as the numerical OR was not available. Most studies reported a positive association between any family history of cardiovascular disease and preeclampsia.

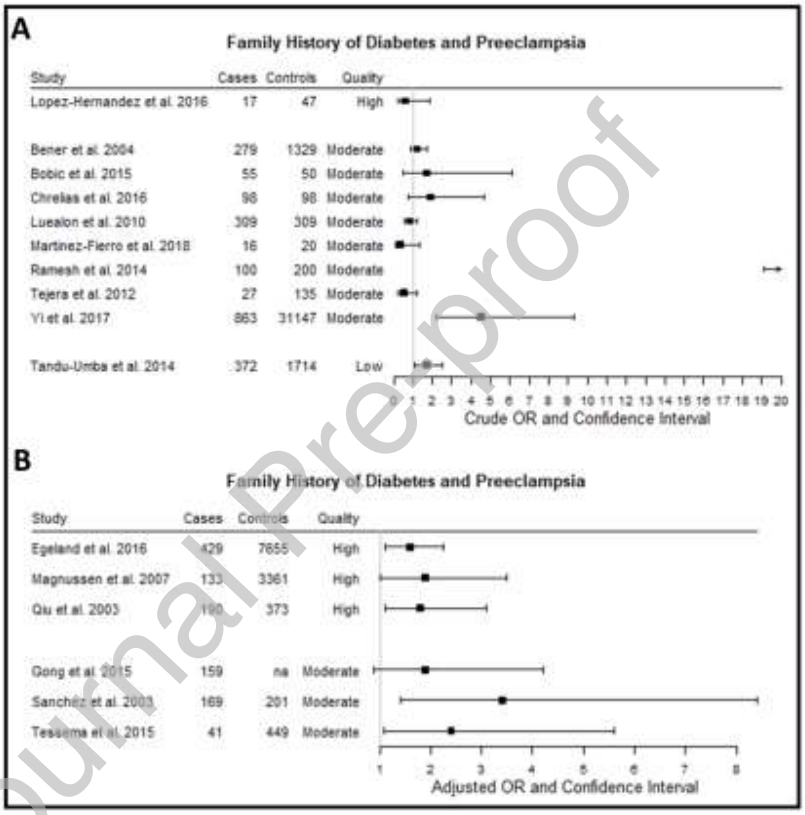

**Figure 4: Forest Plot of Studies Examining Family History of Diabetes.** Thirty studies examined the association between family history of diabetes and preeclampsia. The crude odds ratios (A) and adjusted odds ratios (B) with 95% confidence intervals from studies with a clear definition of preeclampsia and a normotensive control group are presented here. Three studies were excluded for presenting RRs. Three studies with non-significant adjusted ORs were not presented as the numerical OR was not available. Less than half of the studies reported significant associations between family history of diabetes and preeclampsia.

**Supplementary Table 1: Search strategies**

| Database | Search Terms |
|---|---|
| MEDLINE | (Preeclampsia/ OR pregnancy toxemias.mp OR preeclampsia.mp OR pre-eclampsia.mp OR HELLP Syndrome/ OR HELLP*.mp OR Eclampsia/ OR eclampsia.mp OR Hypertension, Pregnancy-Induced/ OR Pregnancy Complications, Cardiovascular/) AND (Risk Factors/ OR risk.mp OR family history.mp OR hereditary.mp OR inherited.mp) AND (exp Hypertension/ OR hypertension.mp OR exp Cardiovascular Diseases/ OR heart disease*.mp OR Diabetes Mellitus, Type 2/ OR type 2 diabetes.mp) |
| EMBASE | (preeclampsia/ OR eclampsia and preeclampsia/ OR eclampsia/ OR pregnancy toxemia/ OR preeclampsia.mp OR pre-eclampsia.mp OR eclampsia.mp OR HELLP Syndrome/ OR HELLP.mp OR maternal hypertension/ OR pregnancy-induced hypertension.mp) AND (risk factor/ OR family history/ OR family history.mp OR hereditary.mp OR inherited.mp) AND (exp hypertension/ OR hypertension.mp OR exp cardiovascular disease OR heart disease*.mp OR exp diabetes mellitus/ OR type 2 diabetes.mp) |
| Cochrane Library | (MH Pre-Eclampsia OR MH Eclampsia OR MH Pregnancy-Induced Hypertension OR preeclampsia OR pre-eclampsia OR pregnancy toxemia OR MH HELLP Syndrome) AND (MH Risk Factors OR risk OR MH Family History OR family history OR hereditary OR inherited) AND (MH Hypertension OR hypertension OR MH Cardiovascular Disease OR MH Heart Diseases OR heart disease OR MH Diabetes Mellitus, Type 2 OR type 2 diabetes) |
| CINAHL/pre-CINAHL | (MESH descriptor: [Pregnancy Induced Hypertension], explode all trees OR preeclampsia OR pre-eclampsia OR pregnancy toxemia OR HELLP Syndrome OR eclampsia) AND (MeSH descriptor: [Risk Factors], explode all trees OR family history OR hereditary OR inherited) AND (MeSH descriptor [Cardiovascular Diseases], explode all trees OR heart disease OR hypertension OR MeSH descriptor [Diabetes Mellitus, Type 2], explode all trees OR type 2 diabetes) |

**Supplementary Table 2: Studies examining associations between family history of hypertension and preeclampsia.**

| *Study* | *Sample size* | *Definition of family history* | *Outcome* | *Adjusted for:* | *Measure of Association* | *Quality of study* |
|---|---|---|---|---|---|---|
| Adam et al. 2011 | 143 cases, 143 controls | Family history of hypertension from structured questionnaire | Preeclampsia | Age, parity, maternal blood group, past history preeclampsia, placental malaria | OR = 5.7 [2.9-11.5] | High (8/10) |
| Aksornph-usitaphong et al. 2013 | 152 early-onset preeclampsia, 297 late-onset preeclampsia, 449 controls | Family history of hypertension from medical records | Preeclampsia including eclampsia and superimposed preeclampsia | Age, BMI, weight gain, female infant, calcium intake, family history diabetes/hypertension | non-significant and not reported for early-onset PE; OR = 18 [6-54] for late-onset PE | High (8/10) |
| Alves et al. 2016 | 41 cases, 82 controls | Family history of hypertension, method of assessment unclear | Preeclampsia developing after 34 weeks | Unadjusted, crude OR calculated from data in the publication | OR = 2.20 [0.72-6.78] | Low (3/10); abstract publication |
| Anorlu et al. 2005 | 128 cases, 280 controls | Family history of hypertension from interview with | Preeclampsia | Age, parity, education, family history hypertension, occupation, weight, home and work | OR = 2.21 [1.17-6.20] | Moderate (7/10) |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | structured form | | environment | | |
| Apostol et al. 2012 | Cohort of women with gestational diabetes with 16 cases, 77 controls | Family history of hypertension from chart review | Pregnancy-induced hypertension in women (unclear) | Unadjusted, crude OR | OR = 3.89 [1.19-12.76] | Low (2/10); abstract publication |
| Barden et al. 2004 | Cohort of women with gestational diabetes with 22 cases, 162 controls | Family history of hypertension in a first or second degree relative from prenatal nurse-administered questionnaire | Preeclampsia | CRP, glucose, family history of gestational diabetes mellitus | OR = 1.64 [1.13-2.41] | High (8/10) |
| Bener et al. 2013 | Cohort of women with 279 cases, 1329 controls | Family history of hypertension from interview with structured questionnaire | Preeclampsia | Unadjusted, crude OR | OR = 1.4 [1.1-1.9] | Moderate (6/10) |
| Bezerra et al. 2010 | 148 cases, 264 controls | Hypertension in mother or sister by medical records and interview of relative | Severe complications of preeclampsia including HELLP and eclampsia | Gestational age, controls matched on age and parity | OR = 1.46 [1.13-1.88] for maternal OR = 2.6 [1.61-4.21] for sibling; OR = 3.65 [1.65- | High (9/10) |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | 8.09] for both maternal and sibling | |
| Cho et al. 2016 | Cohort of women with 6585 cases, 205878 controls | Family history of hypertension from database of pre-pregnancy assessment | Diagnosis of preeclampsia from ICD codes in database | Unadjusted, crude RR calculated from data in the publication | RR = 1.24 [1.16-1.33] | Moderate (6/10) |
| Chrelias et al. 2016 | 98 cases, 98 controls | Family history of hypertension in either parent from medical records | Preeclampsia | Crude OR calculated from presented data, controls matched on age, gestational age and time of delivery | OR = 1.71 [0.97-3.00] | Moderate (7/10) |
| de Carvalho et al. 2006 | Cohort of adolescents with 15 cases, 14 controls | Family history of spontaneous arterial hypertension, method of assessment unclear | Gestational hypertension (gHTN) | Unadjusted crude OR | OR = 10.99 [1.99-60.57] | Low (3/10); |
| Di Martino et al. 2016 | Cohort of women with 43 cases, 937 controls | Family history of hypertension from interview with structured questionnaire | Preeclampsia or gHTN | Unadjusted, crude RR calculated from data in the publication | RR = 1.88 [1.04-3.41] | Low (5/10) |
| Eskenazi et al. | 139 cases, | Family history of | Preeclampsia | Race, employment status, age, parity, | OR = 1.7 [0.92-3.2] | Moderate |

| | | | | | | |
|---|---|---|---|---|---|---|
| 1991 | 132 controls | hypertension from medical records | | BMI, weight gain, smoking, previous preeclampsia, alcohol, year of delivery, marital status, week of gestation at first visit, history of abortion (spontaneous/therapeutic), family history hypertension | | (7/10) |
| Fang et al. 2009 | 150 cases, 150 controls | Family history of hypertension from interview with structured questionnaire | Preeclampsia | Age, alcohol, smoking, exercise, family history hypertension, personal history hypertension in pregnancy, prenatal care | OR = 1.92 [0.87-4.23] | Moderate (7/10) |
| Ganesh Kumar et al. 2010 | 100 cases, 100 controls | Family history of hypertension from medical records | Preeclampsia | BMI, parity, multiple pregnancy, history of hypertension, diabetes or renal disease, family history hypertension | OR = 5.48 [1.09-27.55] | Moderate (7/10) |
| Gong et al. 2015 | 159 cases, Unclear number of controls | Family history of hypertension, unclear method of assessment | Self-reported diagnosis of severe preeclampsia or HELLP | Age, parity | OR = 1.9 [0.8-4.2] | Low (4/10); abstract publication |
| Guerrier et al. 2013 | 419 cases, 1257 controls | Family history of hypertension from interview with structured | Severe preeclampsia or eclampsia | Age less than 20, school attendance, occupation, primiparity, history of preeclampsia, history of hypertension, | OR = 1.2 [0.6-2.3] | High (8/10) |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | questionnaire | | family history of preeclampsia, few antenatal care visits, traditional medicine used in pregnancy | | |
| Hinkosa et al. 2020 | 199 cases, 398 controls | Family history of hypertension from medical records | Hypertension disorders of pregnancy (preeclampsia, gHTN, superimposed preeclampsia, chronic hypertension) | age, rural/urban, marital status, gravida, parity, abortion, multiples, antenatal care, previous hypertension, previous diabetes | OR = 5.04 [2.66-9.56] | Moderate (6/10) |
| Hirashima et al. 2014 | Cohort of women with 35 cases, 1184 controls | Family history of hypertension, method of assessment unclear | Preeclampsia or superimposed preeclampsia | Unadjusted, crude RR calculated from data in the publication | RR = 2.97 [1.55-5.69] | Low (4/10) |
| Hu et al. 2015 | 373 cases, 507 controls | History of hypertension in a mother or sibling from interview with structured questionnaire | Hypertensive disorders of pregnancy (undefined) | Age, residence, education (paternal and maternal), occupation, family history pregnancy-induced hypertension, family history hypertension, CVD, BMI, personal history pregnancy-induced hypertension, smoking, sleep quality, anxiety, relationship with in-laws | OR not reported but non-significant | High (8/10) |
| Huang et al. 2014 | Cohort of women with 84 cases preeclampsia, | Family history of hypertension from antenatal record | Preeclampsia or gHTN, analyzed separately | Unadjusted, crude RR calculated from data in the publication | Preeclampsia: RR = 1.95 [0.49-7.77] gHTN: | Low (5/10) |

| | | | | | | |
|---|---|---|---|---|---|---|
| | 371 cases gHTN 5740 controls | | | | RR = 12.25 [10.10-14.86] | |
| Kahsay et al. 2018 | 110 cases, 220 controls | Family history of hypertension from interview with structured questionnaire | Preeclampsia, gHTN or superimposed preeclampsia | Residence, age, marital status, family history HTN, fruits, vegetables, smoking, BMI, coffee, multiples, gestational diabetes, oral contraceptives | OR = 2.1 [0.7-6.4] | Moderate (6/10) |
| Khader et al. 2007 | 115 cases, 230 controls | Family history of hypertension from interview with structured questionnaire | Preeclampsia | Age, parity, BMI, history of preeclampsia, family history of preeclampsia, family history CVD and periodontal disease; history of abortions, history preterm birth, history C-section, history diabetes, UTI, family history diabetes, family history HTN | OR not reported but not significant | High (8/10) |
| Kiondo et al. 2012 | 207 cases, 352 controls | Family history of hypertension by prenatal interview | Preeclampsia or superimposed preeclampsia | Plasma vitamin C, marital status, distance from hospital, alcohol intake, arm circumference, history of HTN, parity, education level, SES, smoking, HIV, history of diabetes | OR = 2.25 [1.53-3.31] | High (8/10) |
| Kiss et al. 1989 | 256 cases, 263 controls | Family history of hypertension, method | gHTN | Unadjusted, crude OR calculated from data in the publication | OR = 4.55 [1.52-13.64] | Low (4/10) |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | of assessment unclear | | | | |
| Klonoff-Cohen et al. 1996 | 107 cases, 111 controls | Family history of hypertension in a parent, method of assessment unclear | Preeclampsia | Unadjusted, crude OR calculated from data in the publication | OR = 0.79 [0.46-1.36] for maternal; OR = 1.83 [0.97-3.43] for paternal | Moderate (6/10) |
| Kobashi et al. 2004 | 114 cases, 291 controls | Family history of hypertension, method of assessment unclear | Severe preeclampsia | Alleles of two genes, family history of hypertension, BMI and age | OR = 2.2 [1.1-4.5] | High (9/10) |
| Li et al. 2016 | Cohort of women with 111 cases preeclampsia, 338 cases gHTN, 5774 controls | Family history of hypertension from medical records | Preeclampsia or gHTN, analyzed separately | Maternal age, BMI, fetal sex, parity, abortion history, smoking, gestational diabetes, pregnancy complications of cardiac/renal/diabetes, reproductive tract infection, season of delivery, approximated socioeconomic status | Preeclampsia: OR = 1.14 [0.3-4.44] gHTN: OR = 1.97 [0.97-4.01] | Moderate (7/10) |
| Lopez-Hernandez et al. 2016 | 17 cases, 47 controls | Family history of hypertension, method of assessment unclear | Preeclampsia | Unadjusted, crude OR calculated from data in the publication but cases/controls matched on age, parity, BMI, personal history preeclampsia and family history preeclampsia | OR = 1.84 [0.52-6.55] | High (8/10) |

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|---|---|---|---|---|---|---|
| Lucovnik et al. 2018 | Cohort of twin pregnancies with 71 cases preeclampsia, 36 cases gHTN, 1626/1661 controls | Family history of hypertension from national database | Preeclampsia or gHTN, analyzed separately | Parity, age, BMI, smoking, diabetes, gestational diabetes, fetal sex, family history of hypertension, assisted reproduction | Preeclampsia: OR = 1.0 [0.6-1.9] gHTN: OR = 2.6 [1.3-5.1] | Moderate (6/10) |
| Luealon et al. 2010 | 309 cases, 309 controls | Family history of hypertension, method of assessment unclear | Preeclampsia/severe preeclampsia | Unadjusted, crude OR calculated from data in the publication | OR = 1.37 [0.90-2.08] | Moderate (6/10) |
| Mabuchi et al. 2016 | Cohort of women with 62 cases preeclampsia, 124 cases gHTN 1916 controls | Family history of hypertension, method of assessment unclear | Preeclampsia or gHTN, analyzed separately | Unadjusted, crude OR | Preeclampsia: OR = 1.34 [0.78-2.24] gHTN: OR = 1.38 [0.93-2.03] | Low (5/10) |
| Magnussen et al. 2007 | Cohort of women with 133 cases 3361 controls | Family history of hypertension from questionnaire | Diagnosis of preeclampsia reported in national birth registry | Maternal age at birth, duration between evaluation and birth, parity, previous preeclampsia, smoking | OR = 2.0 [1.3-2.9] | High (9/10) |
| Mahomed et al. 1998 | 200 cases, 200 controls | Family history of hypertension in mother or sister from postpartum interview | Preeclampsia with or without eclampsia | Age, parity, twin gestation, chronic hypertension | OR = 2.3 [1.3-3.6] maternal OR = 2.9 [1.4-5.7] sibling OR = 11.2 [2.4-51.5] both | High (9/10) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Martinez-Fierro et al. 2018 | 16 cases, 20 controls | Family history of hypertension from questionnaire | Preeclampsia | Unadjusted, crude OR calculated from data in the publication | OR = 1.44 [0.29-7.25] | Moderate (6/10) |
| Maruta et al. 2017 | Cohort of women with 25 cases, 186 controls | Family history of hypertension, method of assessment unclear | Preeclampsia, gHTN, superimposed preeclampsia | age, BMI, smoking, parity, family history hypertension, l-arginine, homocysteine and ADMA, | OR = 2.36 [0.55-9.14] | Moderate (6/10) |
| Maruyama et al. 2004 | 84 cases, 160 controls | Family history of hypertension in a parent, grandparent, aunt, uncle or sibling, method of assessment unclear | Preeclampsia | Unadjusted, crude OR calculated from data in the publication | OR = 2.47 [1.32-4.62] | Low (4/10) |
| Mayret-Mesquiti et al. 2007 | 27 cases, 47 controls | Family history of hypertension, method of assessment unclear | Preeclampsia or gHTN | Unadjusted, crude OR calculated from data in the publication | OR = 1.10 [0.39-3.13] | Low (4/10) |
| Muto et al. 2016 | Cohort of women with 166 cases, 1820 controls | Family history of hypertension in first or second degree relative from questionnaire | Preeclampsia or gHTN | Unclear | OR = 1.67 [1.04-2.69] for nulliparous OR = 1.21 [0.69-2.06] for multiparous | High (8/10) |

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|---|---|---|---|---|---|---|
| Nalogowska-Glosnicka et al. 2000 | 126 cases, 150 controls | Family history of hypertension in a parent from questionnaire sent to parents | gHTN | Unadjusted, crude OR calculated from data in the publication | OR = 2.71 [1.56-4.69] | Moderate (7/10) |
| Nanjunden et al. 2011 | 100 cases, 100 controls with gHTN | Family history of hypertension from questionnaire | Preeclampsia or superimposed preeclampsia | Overweight, hypothyroidism, multigravida, previous PE, inadequate antenatal care, passive smoking, lower SES, employment during pregnancy, non-availability of help at home, non-availability of resting hours, joint family | OR = 8.92 [2.8-28.39] | Moderate (6/10) |
| Ndao et al. 2009 | 101 cases preeclampsia 69 cases gHTN 241 controls | Family history of hypertension in parents from interview and review of parent's medical records | Preeclampsia or gHTN analyzed separately | Parity, illiteracy, marital status, past poor pregnancy outcome, residence, living with partner <2 years, number of antenatal visits, FmHx HTN, placental malaria, period of delivery | Preeclampsia: OR = 1.9 [1.1-3.2] gHTN: OR = 2.8 [1.5-5.3] | Moderate (7/10) |
| Ness et al. 2003 | Cohort of women with 85 cases preeclampsia, 142 cases gHTN 1984 controls | Family history of hypertension in a first degree relative by prenatal interview | Preeclampsia or gHTN analyzed separately | Age, BMI | Preeclampsia: RR = 1.5 [1.0-2.5] gHTN: 1.2 [0.8-1.8] | High (9/10) |

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|---|---|---|---|---|---|---|
| Ohkuchi et al. 2012 | 30 cases, 128 controls | Family history of hypertension, method of assessment unclear | Preeclampsia or superimposed preeclampsia | past history gestational hypertension/preeclampsia family history hypertension, mean blood pressure, BMI, bilateral notching, sFlt/PGF ratio, plasma HSD17b1 | Adjusted OR not reported but not significant | Moderate (7/10) |
| Owiredu et al. 2012 | 30 cases preeclampsia, 70 cases gHTN 50 controls | Family history of hypertension from interview with structured questionnaire | Preeclampsia or gHTN, analyzed separately | Age, family history HTN, condom use, contraceptive use, change of partner | Preeclampsia: OR = 9.7 [2.2-42.6] gHTN: OR = 7.0 [2.2-22.7] | High (8/10) |
| Qiu et al. 2003 | 190 cases, 373 controls | Family history of hypertension in a parent or sibling by postpartum interview | Preeclampsia | Age, race, parity, household income, BMI | OR = 1.7 [1.2-2.6] | High (8/10) |
| Ramesh et al. 2014 | 100 cases, 200 controls | Family history of hypertension from semi-structured questionnaire | Preeclampsia | Crude unadjusted OR, controls matched on parity | OR = 16.71 [9.0-31.0 | Moderate (7/10) |
| Reyes et al. 2012 | 201 cases, 201 controls | Family history of hypertension in a first degree relative from medical | Preeclampsia | Primigravidity, stress at work, stress at home, use of condoms, vitamin supplementation, folic acid supplementation, sibling with | Adjusted OR not reported but not significant | High (9/10) |

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| | | records | | preeclampsia, family history hypertension, dyslipidemia, CVD, diabetes, or stroke, BMI, leukocytes count, HDL, LDL, triglycerides, glucose, CRP | | |
| Rigo et al. 2006 | 162 cases, 521 controls | Family history of hypertension in a parent before age 50 by postpartum interview, confirmed by medical records | Severe preeclampsia | Age, BMI, smoking | OR = 3.81 [2.50-5.80] | High (10/10) |
| Saeed et al. 2011 | 218 cases, 371 controls | Family history of hypertension, method of assessment unclear | Preeclampsia or gHTN | Age, parity, BMI, family history hypertension, delivery status, ICU stay | OR = 3.97 [2.65-5.96] | Moderate (6/10) |
| Sanchez et al. 2003 | 169 cases, 201 controls | Family history of hypertension in a parent | Preeclampsia | Age, parity and pre-pregnancy BMI | OR= 1.2 [0.7-2.2] | High (8/10); abstract publication |
| Shamsi et al. 2010 | 131 cases, 262 controls | Family history of hypertension from postpartum interview | Preeclampsia | Age, SES, UTI, family history diabetes, maternal weight, Rh factor | OR = 2.06 [1.27-3.35] | High (8/10) |
| Singh et | Cohort of | Family | Preeclampsia, | Unadjusted, crude | RR = 1.82 | Low |

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| al. 2014 | women with 36 cases, 180 controls | history of hypertension from interview with structured questionnaire | gHTN, superimposed preeclampsia, chronic hypertension | RR calculated from data in the publication | [0.98-3.40] | (5/10) |
| Stone et al. 1994 | 70 cases, 18964 controls | Family history of hypertension, method of assessment unclear | Severe preeclampsia | Unadjusted, crude OR calculated from data in the publication | OR = 1.16 [0.66-2.06] | Low (5/10) |
| Sun et al. 2010 | 105 cases, 103 controls | Family history of hypertension from method of assessment unclear | Preeclampsia | Unadjusted, crude OR calculated from data in the publication | OR = 3.03 [1.45-6.33] | Moderate (7/10) |
| Sun et al. 2018 | 276 cases, 229 controls | Family history of hypertension method of assessment unclear | Preeclampsia | Unadjusted, crude OR calculated from data in the publication | OR = 2.99 [1.90-4.71] | Moderate (7/10) |
| Taguchi et al. 2014 | Cohort of women with twin gestations with 165 cases, 577 controls | Family history of hypertension from medical records | Preeclampsia, gHTN or superimposed preeclampsia | Monochorionic placenta, primipara, maternal age, IVF, BMI, smoking, family history hypertension | OR = 1.5 [1.03-2.17] | Moderate (6/10) |
| Tandu-Umba et al. 2014 | 372 cases, 1714 controls | Family history of hypertension, method | Preeclampsia or eclampsia (undefined) | Age >35, HTN in family, previous CS, previous macrosomia, previous PROM, | OR =0.5 [0.3-0.9] | Moderate (7/10) |

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|---|---|---|---|---|---|---|
| | | of assessment unclear | | previous stillbirth, obesity | | |
| Tebeu et al. 2011 | 152 cases, 414 controls | Family history of hypertension in a parent or sibling, method of assessment unclear | gHTN, chronic hypertension, preeclampsia, superimposed preeclampsia | Education, number of deliveries, history of hypertension in siblings, history of hypertension in pregnancy | OR not reported but not significant for paternal; OR = 3.6 [1.6-8.5] for sibling | Low (5/10) |
| Tejera et al. 2012 | 27 cases, 135 controls | Family history of hypertension in a parent from interview | Preeclampsia (undefined) | Unadjusted, crude OR calculated from data in the publication | OR = 3.09 [1.29-7.40] | Moderate (6/10) |
| Tessema et al. 2015 | 41 cases, 449 controls | Family history of hypertension from interview with structured questionnaire | Preeclampsia | Age, marital status, chronic hypertension, family history hypertension, family history diabetes | OR = 7.19 [3.4-15.2] | Moderate (7/10) |
| Thadhani et al. 1999 | Cohort of women with 86 cases preeclampsia, 216 cases gHTN 14960 controls | Family history of hypertension in a parent from pre-pregnancy questionnaire | Preeclampsia or gHTN, analyzed separately | Unadjusted, crude RR calculated from data in the publication | Preeclampsia: RR = 1.45 [0.92-2.29] for maternal; RR = 0.86 [0.54-1.41] for paternal gHTN: RR = 1.43 [1.08-1.90] for maternal, RR = 1.31 [0.99- | Moderate (7/10) |

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| | | | | | 1.73] for paternal | |
| Vieira et al. 2018 | Cohort of women with obesity with 59 cases, 735 controls | Family history of hypertension in a first degree relative, method of assessment unclear | Preeclampsia | Unadjusted, crude OR | OR = 1.48 [0.87-2.51] | Low (5/10) |
| Vigeh et al. 2004 | 55 cases, 55 controls | Family history of hypertension, method of assessment unclear | Preeclampsia or gHTN | Unadjusted, crude OR calculated from data in the publication | OR = 1.95 [0.82-4.64] | Moderate (6/10) |
| Walle et al. 2019 | 71 cases, 351 controls | Family history of hypertension from interview with structured questionnaire | Preeclampsia, gHTN or "gestational proteinuria" | Age, education, income, age at first pregnancy, age at menarche, multiplicity, history of chronic hypertension, family history hypertension, smoking, alcohol | OR = 7.77 [3.04-19.62] | Moderate (6/10) |
| Wandabwa et al. 2010 | 143 cases, 500 controls | Family history of hypertension from interview | Severe preeclampsia | Distance from home to hospital, job, type of house, transport used to get to hospital, method of treatment payment, age and asking for permission, family history hypertension | OR= 1.9 [1.2-2.9] | High (8/10) |
| Wang et al. 2019 | 46 cases, 138 controls | Family history of hypertension, | Severe preeclampsia | Coagulation index, BMI, family history hypertension, age | OR = 3.79 [1.21-11.48] | High (8/10) |

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|---|---|---|---|---|---|---|
| | | method of assessment unclear | | | | |
| Wang et al. 2018 | 553 cases, 9675 controls | Family history of hypertension from interview with structured questionnaire | Preeclampsia or gHTN | Unadjusted, crude OR calculated from data in the publication | OR = 1.82 [1.49-2.24] | Low (5/10) |
| Ye et al. 2014 | 5869 cases, 106517 controls | Family history of hypertension in a parent, method of assessment unclear | Preeclampsia, gHTN, chronic hypertension, superimposed preeclampsia | Age, gravidity, parity, history of abortion, twin pregnancy, education, alcohol, family history HTN, family history diabetes, BMI, SBP, DBP, ABO blood type, GDM | OR = 2.84 [2.37-3.39] | Moderate (7/10) |
| Yi et al. 2017 | 863 cases, 31147 controls | Family history of hypertension from medical records | Preeclampsia | Unadjusted, crude OR | OR = 7.66 [3.35-17.50] | Low (5/10) |
| Youssef et al. 2011 | Cohort of women with 13 cases, 515 controls | Family history of hypertension, method of assessment unclear | Preeclampsia | Crude RR calculated from presented data | RR = 3.92 [0.56-27.55] | Low (5/10) |
| Yu et al. 2014 | Cohort of women with 30 cases, 867 controls | Family history of hypertension from interview with questionnaire | Self-reported early-onset preeclampsia | Age, family history hypertension, history of abortion, history of HTN/diabetes/nephrosis, BMI, primigravidity, high risk co- | OR = 6.77 [2.92-15.74] | Moderate (6/10) |

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| | | | | efficient for trisomy 21 and 13 | | |
| Zhou et al. 2015 | 53 cases, 106 controls | Family history of hypertension from medical records | Preeclampsia or gHTN | Family history hypertension, gravidity, BMI, concentration of TRAIL, age, gestational age | Adjusted OR not reported but not significant | Moderate (7/10) |

**Supplementary Table 3: Studies examining associations between family history of cardiovascular disease and preeclampsia.**

| ***Study*** | ***Sample size*** | ***Definition of family history*** | ***Definition of outcome*** | ***Adjusted for:*** | ***Measure of Association*** | ***Quality of Study*** |
|---|---|---|---|---|---|---|
| Alves et al. 2013 | Cohort of women with 342 cases, 6610 controls | Stroke or myocardial infarction in a parent or sibling from interview with questionnaire | Chronic hypertension, gHTN or preeclampsia | Age, education, newborn sex, smoking status, BMI, weight gain during pregnancy | Primipara: PR = 1.33 [0.92-1.91]; Multipara: PR = 1.48 [1.00-2.17] | Moderate (7/10) |
| Barden et al. 2004 | Cohort of women with gestational diabetes with 22 cases, 162 controls | Family history of heart disease from questionnaire | Preeclampsia | Unadjusted, crude RR calculated from data in the publication | RR = 0.38 [0.09 -1.57] | Moderate (6/10) |
| Blaauw et al. 2006 | 22 cases, 22 controls | Family history of cardiovascular disease in first or | Preeclampsia, including HELLP | Unadjusted, crude OR calculated from data in the publication | OR = 2.10 [0.63-7.03] | Moderate (6/10) |

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| | | second degree relative before 55 in men or 65 in women from questionnaire | | | | |
| Bobic et al. 2015 | 55 cases, 50 controls | Family history of "cardiovascular morbidity", method of assessment unclear | Preeclampsia | Unadjusted, crude OR calculated from data in the publication | OR = 1.54 [0.54 -4.33] | Moderate (7/10) |
| Egeland et al. 2016 | Cohort of women with 429 cases preeclampsia, 237 cases gHTN, 7655 controls | Family history of myocardial infarction before age 60 in first degree family member from pre-pregnancy health surveys linked to birth registry data | Preeclampsia or gHTN analyzed separately | Mother as a cluster (multiple pregnancies included for an individual woman) | Preeclampsia: OR = 1.8 [1.31-2.39] gHTN: OR = 1.1 [0.69-1.70] | High (8/10) |
| Ehrenthal et al. 2015 | Cohort of women with 31 cases, 40 controls | Family history of cardiovascular disease in a first degree relative from interview with questionnaire | Preeclampsia or gestational hypertension | Unadjusted, crude OR calculated from data in the publication | OR = 0.32 [0.11-0.92] | Low (5/10) |
| Hu et al. 2015 | 373 cases, 507 controls | Family history of cardiovascular disease in a mother or sibling from | Hypertensive disorders of pregnancy (undefined) | Age, residence, education (paternal and maternal), occupation, | OR = 6.18 [2.37-16.14] | Moderate (7/10) |

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|---|---|---|---|---|---|---|
| | | interview with questionnaire | | family history pregnancy-induced hypertension, family history hypertension, CVD, BMI, personal history pregnancy-induced hypertension, smoking, sleep quality, anxiety, relationship with in-laws | | |
| Khader et al. 2007 | 115 cases, 230 controls | Family history of cardiovascular disease from interview with questionnaire | Preeclampsia | Age, parity, BMI, history of preeclampsia, family history of preeclampsia, family history CVD and periodontal disease; history of abortions, history preterm birth, history C-section, history diabetes, UTI, family history diabetes, family history HTN | OR = 2.82 [1.22-6.51] | Moderate (7/10) |
| Magnussen et al. 2007 | Cohort of women with 133 cases, 3361 controls | Family history of cardiovascular disease from questionnaire | Diagnosis of preeclampsia reported in national birth | Maternal age at birth, duration between evaluation and birth, parity, | OR = 1.7 [1.0-3.0] | High (8/10) |

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|---|---|---|---|---|---|---|
| | | | registry | previous preeclampsia, smoking | | |
| Ness et al. 2003 | Cohort of women with 85 cases preelcampsia, 142 cases gHTN, 1984 controls | Cardiovascular disease or stroke in first degree relative by prenatal interview | Preeclampsia or gHTN, analyzed separately | Age, BMI | Preeclampsia: RR = 0.9 [0.5-1.7] gHTN: RR = 1.2 [0.7-1.9] | High (9/10) |
| North et al. 2011 | Cohort of women with 186 cases, 3343 controls | Family history of coronary artery disease in father from interview | Preeclampsia | Age, MAP, BMI, family history preeclampsia, family history cardiovascular disease, patient's birth weight, vaginal bleeding, previous miscarriage, less than 12 months to conceive, fruit intake, alcohol, smoking | OR = 1.9 [1.2-2.8] | High (10/10) |
| Reyes et al. 2012 | 162 cases, 521 controls | Family history of cardiovascular disease in a first degree relative from medical records | Preeclampsia | Primigravidity, stress at work, stress at home, use of condoms, vitamin supplementation, folic acid supplementation, sibling with preeclampsia, family history hypertension, | Adjusted OR not reported but not significant | High (9/10) |

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|---|---|---|---|---|---|---|
| | | | | dyslipidemia, CVD, diabetes, or stroke, BMI, leukocytes count, HDL, LDL, triglycerides, glucose, CRP | | |
| Rigo et al. 2006 | 162 cases, 521 controls | Family history of myocardial infarction in any parent before age 50 from interview, confirmed by medical records | Severe preeclampsia | Age, BMI, smoking | OR = 3.65 [1.75-7.59] | High (10/10) |
| Serrano et al. 2020 | 3086 cases, 3888 controls | Family history of myocardial infarction or stroke in a parent from interview with questionnaire | Preeclampsia, | Age, ethnicity | OR = 1.58 [1.24-2.01] | High (8/10) |



**Supplementary Table 4: Studies examining associations between family history of diabetes and preeclampsia.**

| ***Study*** | ***Sample size*** | ***Definition of family history*** | ***Definition of outcome*** | ***Adjusted for:*** | ***Measure of Association*** | ***Quality of study*** |
|---|---|---|---|---|---|---|
| Aksornph-usitaphon | 152 early PE, | Family history of | Preeclampsia including | Age, BMI, weight gain, | OR =2.5 [1.1-5.6] | High (8/10) |

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|---|---|---|---|---|---|---|
| g et al. 2013 | 297 late PE, 449 controls | diabetes from medical records | eclampsia and superimposed preeclampsia | female infant, calcium intake, family history diabetes/hypertension | for early-onset PE OR = 2.7 [1.6-4.4] for late-onset PE | |
| Barden et al. 2004 | Cohort of women with gestational diabetes with 22 cases, 162 controls | Family history of diabetes from prenatal questionnaire | Preeclampsia | Unadjusted, crude RR calculated from data in the publication | RR = 2.04 [0.79-5.28] | Moderate (6/10) |
| Bener et al. 2013 | Cohort of women with 279 cases, 1329 controls | Family history of diabetes from interview with structured questionnaire | Preeclampsia | Unadjusted, crude OR | OR = 1.2 [0.9-1.7] | Moderate (6/10) |
| Bobic et al. 2015 | 55 cases, 50 controls | Family history of diabetes, method of assessment unclear | Preeclampsia | Unadjusted, crude OR calculated from data in the publication | OR = 1.68 [0.46-6.11] | Moderate (6/10) |
| Chrelias et al. 2016 | 98 cases, 98 controls | Family history of diabetes in either parent from medical records | Preeclampsia | Unadjusted crude OR calculated from data in the publication, controls matched on age, gestational age and time of delivery | OR = 1.88 [0.75-4.70] | Moderate (7/10) |
| Egeland et al. 2016 | Cohort of women with 429 cases preeclampsia, | Family history of diabetes before age 60 in first | Preeclampsia or gHTN analyzed separately | Mother as a cluster (multiple pregnancies included for an individual woman) | Preeclampsia: OR = 1.6 [1.12-2.25] gHTN: OR = 2.1 | High (8/10) |

| | | | | | | |
|---|---|---|---|---|---|---|
| | 237 cases gHTN, 7655 controls | degree family member from pre-pregnancy health surveys linked to birth registry data | | | [1.39-3.09] | |
| Gong et al. 2015 | 159 cases, Unclear number of controls | Family history of diabetes, unclear method of assessment | Self-reported diagnosis of severe preeclampsia or HELLP | Age, parity | OR = 1.9 [0.9-4.2] | Low (4/10); abstract publication |
| Hu et al. 2015 | 373 cases, 507 controls | Family history of diabetes in a mother or sibling from interview with structured questionnaire | Hypertensive disorders of pregnancy (undefined) | Age, residence, education (paternal and maternal), occupation, family history pregnancy-induced hypertension, family history hypertension, CVD, BMI, personal history pregnancy-induced hypertension, smoking, sleep quality, anxiety, relationship with in-laws | OR not reported but non-significant | Moderate (7/10) |
| Huang et al. 2014 | Cohort of women with 84 cases preeclampsia, 371 cases gHTN | Family history of diabetes from antenatal record | Preeclampsia | Unadjusted, crude RR calculated from data in the publication | Preeclampsia: RR = 4.37 [0.65-29.53] | Low (5/10) |

| | | | | | | |
|---|---|---|---|---|---|---|
| | 5740 controls | | | | | |
| Khader et al. 2007 | 115 cases, 230 controls | Family history of diabetes from interview with questionnaire | Preeclampsia | Age, parity, BMI, history of preeclampsia, family history of preeclampsia, family history CVD and periodontal disease; history of abortions, history preterm birth, history C-section, history diabetes, UTI, family history diabetes, family history HTN | Adjusted OR not reported but not significant | High (8/10) |
| Lopez-Hernandez et al. 2016 | 17 cases, 47 controls | Family history of diabetes, method of assessment unclear | Preeclampsia | Unadjusted, crude OR calculated from data in the publication but cases/controls matched on age, parity, BMI, personal history preeclampsia and family history preeclampsia | OR = 0.60 [0.20-1.84] | High (8/10) |
| Luealon et al. 2010 | 309 cases, 309 controls | Family history of diabetes, method of assessment unclear | Preeclampsia/severe preeclampsia | Unadjusted, crude OR calculated from data in the publication | OR = 0.82 [0.56-1.21] | Moderate (6/10) |
| Magnussen et al. 2007 | Cohort of women with 133 cases 3361 controls | Family history of diabetes from questionnaire | Diagnosis of preeclampsia reported in national birth registry | Maternal age at birth, duration between evaluation and birth, parity, previous preeclampsia, smoking | OR = 1.9 [1.0-3.5] | High (8/10) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Martinez-Fierro et al. 2018 | 16 cases, 20 controls | Family history of diabetes from questionnaire | Preeclampsia | Unadjusted, crude OR calculated from data in the publication | OR =0.33 [0.08-1.36] | Moderate (6/10) |
| Maruta et al. 2017 | Cohort of women with 25 cases, 186 controls | Family history of diabetes, method of assessment unclear | Preeclampsia, gHTN, superimposed preeclampsia | Unadjusted, crude RR calculated from data in the publication | RR = 0.58 [0.18-1.85] | Low (4/10) |
| Mayret-Mesquiti et al. 2007 | 27 cases, 47 controls | Family history of diabetes, method of assessment unclear | Preeclampsia or gHTN | Unadjusted, crude OR calculated from data in the publication | OR = 3.50 [1.27-9.62] | Low (4/10) |
| Nanjundan et al. 2011 | 100 cases, 100 controls with gestational hypertension | Family history of diabetes from questionnaire | Preeclampsia or superimposed preeclampsia | Unadjusted, crude OR calculated from data in the publication | OR = 0.67 [0.32-1.37] | Low (4/10) |
| Ness et al. 2003 | Cohort of women with 85 cases preeclampsia, 142 cases gHTN 1984 controls | Family history of diabetes in a first degree relative by prenatal interview | Preeclampsia or gHTN analyzed separately | Age, BMI | Preeclampsia: RR = 1.3 [0.7-2.3] gHTN: RR = 1.3 [0.9-2.1] | High (9/10) |
| Qiu et al. 2003 | 190 cases, 373 controls | Family history of diabetes in a parent or sibling by postpartum interview | Preeclampsia | Age, race, parity, household income, BMI | OR = 1.8 [1.1-3.1] | High (8/10) |
| Ramesh et | 100 cases, | Family | Preeclampsia | Crude | OR = | Moderat |

| | | | | | | |
|---|---|---|---|---|---|---|
| al. 2014 | 200 controls | history of diabetes from semi-structured questionnaire | | unadjusted OR, controls matched on parity | 44.98 [19.1-105.8] | e (6/10) |
| Reyes et al. 2012 | 201 cases, 201 controls | Family history of diabetes in a first degree relative from medical records | Preeclampsia | Primigravidity, stress at work, stress at home, use of condoms, vitamin supplementation, folic acid supplementation, sibling with preeclampsia, family history hypertension, dyslipidemia, CVD, diabetes, or stroke, BMI, leukocytes count, HDL, LDL, triglycerides, glucose, CRP | Adjusted OR not reported but not significant | High (9/10) |
| Sanchez et al. 2003 | 169 cases, 201 controls | Family history of diabetes in a parent | Preeclampsia | Age, parity and pre-pregnancy BMI | OR= 3.4 [1.4-8.4] | Moderate (7/10); abstract publication |
| Shamsi et al. 2010 | 131 cases, 262 controls | Family history of diabetes from interview | Preeclampsia | Age, SES, UTI, family history diabetes, maternal weight, Rh factor | Adjusted OR not reported but not significant | High (8/10) |
| Shargorodsky et al. 2017 | Cohort of women with 31 cases, 308 controls | Family history of diabetes from medical records | Preeclampsia or gestational hypertension | Age, BMI, family history diabetes, weight gain | OR = 1.56 [0.80-3.05] | Moderate (6/10) |
| Singh et al. 2014 | Cohort of women with 36 | Family history of diabetes | Preeclampsia, gHTN, superimposed | Unadjusted, crude RR calculated from | RR = 1.37 [0.55-3.45] | Low (5/10) |

| | | | | | | |
|---|---|---|---|---|---|---|
| | cases, 180 controls | from interview with structured questionnaire | preeclampsia, chronic hypertension | data in the publication | | |
| Tandu-Umba et al. 2014 | 372 cases, 1714 controls | Family history of diabetes, method of assessment unclear | Preeclampsia or eclampsia (undefined) | Unadjusted, crude OR calculated from data in the publication | OR = 1.7 [1.1-2.5] | Low (5/10) |
| Tejera et al. 2012 | 27 cases, 135 controls | Family history of diabetes in a parent from interview | Preeclampsia (undefined) | Unadjusted, crude OR calculated from data in the publication | OR = 0.50 [0.20-1.21] | Moderate (6/10) |
| Tessema et al. 2015 | 41 cases, 449 controls | Family history of diabetes from interview with structured questionnaire | Preeclampsia | Age, marital status, chronic hypertension, family history hypertension, family history diabetes | OR = 2.4 [1.09-5.6] | Moderate (7/10) |
| Ye et al. 2014 | 5869 cases, 106517 controls | Family history of diabetes in a parent, method of assessment unclear | Preeclampsia, gHTN, chronic hypertension, superimposed preeclampsia | Age, gravidity, parity, history of abortion, twin pregnancy, education, alcohol, family history HTN, family history diabetes, BMI, SBP, DBP, ABO blood type, GDM | OR = 1.60 [1.19-2.15] | Moderate (7/10) |
| Yi et al. 2017 | 863 cases, 31147 controls | Family history of diabetes from medical records | Preeclampsia | Unadjusted, crude OR | OR = 4.49 [2.17-9.28] | Moderate (6/10) |

**Supplementary Table 5: Studies examining associations between composite family history exposures and preeclampsia.**

| *Study* | *Sample size* | *Definition of family history* | *Outcome* | *Adjusted for:* | *Measure of Association* | *Quality of study* |
|---|---|---|---|---|---|---|
| Panova et al. 2018 | Cohort of women with chronic hypertension with 230 cases, 318 controls | Composite of family history of hypertension or cardiovascular disease from medical records | Superimposed preeclampsia | Unadjusted, crude RR | RR = 2.2 [1.3-3.9] | Low (4/10) |
| Parker et al. 2012 | Cohort of women with 103 cases, 809 controls | Composite of family history of hypertension, dyslipidemia, heart attack, stroke, angina or vascular surgery in father, method of assessment unclear | Preeclampsia or superimposed preeclampsia | Age, BMI, smoking in pregnancy, personal CVD or risk factors | OR = 1.66 [1.16-2.36] | High (8/10); abstract publication |
| Pralhad et al. 2013 | 100 cases, 100 controls | Composite of family history of either hypertension or diabetes from interview with questionnaire | gHTN | Unadjusted, crude OR calculated from data in the publication | OR = 1.24 [0.59-2.63] | Low (5/10) |



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