**Pre-eclampsia is associated with a two-fold increase in diabetes: a systematic review and meta-analysis**

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**Abstract**

*Aims/hypothesis*:Pre-eclampsia is a pregnancy-specific multi-system disorder and a state of physiological insulin resistance. Our aim is to systematically evaluate and quantify the evidence on the relationship between pre-eclampsia and the future risk of diabetes.

*Methods*:We conducted a systematic review and meta-analysis of studies that evaluated diabetes in women with and without pre-eclampsia. We performed a systematic search of MEDLINE and EMBASE to identify relevant studies. Independent double data extractions were conducted by four reviewers. Random effects meta-analysis was used to estimate the risk of future diabetes following pre-eclampsia.

*Results*: Twenty-one studies were identified with over 2.8 million women including >72,000 women with pre-eclampsia. Meta-analysis of studies that adjusted for potential confounders demonstrated that pre-eclampsia was independently associated with an increased risk of future diabetes (risk ratio (RR) 2.37, 95% CI 1.89, 2.97). This risk appeared in studies that followed up women from <1 year (RR 1.97, 95% CI 1.35, 2.87) and persisted to over 10 years post-partum (RR 1.95, 95% CI 1.28, 2.97). After adjusting for BMI or gestational diabetes, pre-eclampsia was linked with an increased risk of future diabetes (RR 2.38, 95% CI 1.74, 3.24) or (RR 2.36, 95% CI 1.94, 2.88), respectively.

*Conclusions/interpretation*:Pre-eclampsia is independently associated with a two-fold increase in future diabetes. Our study highlights the importance of clinical risk assessment for the future development of diabetes in women with pre-eclampsia. We recommend detailed evaluation of a screening programme for diabetes in this high-risk population.

**Abbreviations**

aRR - Adjusted risk ratio

BMI - Body mass index

FINDRISC - Finnish Diabetes Risk Score

ISSHP - International Society of the Studies of Hypertension in Pregnancy

RR - Risk ratio

**Introduction**

Pre-eclampsia is a pregnancy-specific multi-system disorder affecting 5–8% of pregnancies [1], frequently manifested as new-onset hypertension and proteinuria. It is the commonest cause of severe perinatal morbidity and is responsible for more than 50,000 maternal deaths per annum globally [2]. Pregnancy is known to be a state of physiological insulin resistance and relative glucose intolerance [3]. Postnatally, the insult to the cardiovascular and renal systems often persist in pre-eclampsia, with insulin resistance [4], diffuse vascular endothelial dysfunction [5], and inflammatory factor activation [6] reported, although it is unclear whether these are pre-existing conditions prior to the pregnancy or are longer-term sequelae of pre-eclampsia. Many of these pathophysiological mechanisms are also linked to the future development of diabetes [7]. Furthermore, lower insulin sensitivity and higher insulin levels have been found in women with previous history of pre-eclampsia [8].

It remains controversial whether pre-eclampsia has long-term metabolic sequelae and is an independent risk factor for the future development of diabetes, as it is difficult to separate pre-eclampsia from cofounding factors that are associated with future incident diabetes. The existing literature provides conflicting data with some studies showing significant increases in risk of future diabetes [9, 10], whilst others have not observed such relationships [11, 12]. Many of the studies that have focussed on the association between pre-eclampsia and future incident diabetes, report limited clinical details of the cohorts studied, have not adjusted for body mass index (BMI) [9], family history of diabetes [10], or other factors that are known to increase the future risk of incident diabetes hence raising the potential for unmeasured / unreported confounders contributing to the associations reported. This systematic review and meta-analysis quantifies the risk of diabetes in later life following pre-eclampsia in pregnancy. Here we provide an overview of the studies, and the association between pre-eclampsia and future incident diabetes.

**Methods**

*Eligibility criteria*

We selected studies that evaluated diabetes in women with and without pre-eclampsia. Diabetes could be type 1, type 2, any diabetes and use of diabetic medications such as insulin or oral antidiabetic agents. There was no restriction on the definition of pre-eclampsia. Included studies had to have at least two groups (one with pre-eclampsia and one without pre-eclampsia) and also provide results that allowed risk estimates to be calculated. Studies were included if they evaluated some form of risk or odds (relative risk, risk ratio, hazard ratio or odds ratio, etc.) which measured the association between diabetes among patients with pre-eclampsia and those without pre-eclampsia or crude results which enabled calculation of a risk ratio. Crude results that met these criteria had to evaluate diabetes cases/total participants with pre-eclampsia or diabetes cases/total participants without pre-eclampsia. We planned to contact authors to clarify results where the data reported was uncertain but all the studies which met the inclusion criteria had clear reporting of results. There was no restriction based on study design or cohort type. We excluded publications that were not published in the English language.

*Data sources and searches*

We searched MEDLINE and EMBASE using OVID SP for studies from 2005 to current in August 2015 (see Appendix 1 for comprehensive search terms). This is because the diagnostic criteria for both pre-eclampsia [13] and diabetes [14] were changed in 2001 and 2006, respectively. The relevant primary studies for inclusion on this study were drawn from a comprehensive programme of evidence synthesis which explored the association between pre-eclampsia and adverse cardiovascular or metabolic outcomes. We also examined the bibliography of relevant studies and reviews for additional studies that met the inclusion criteria.

*Study selection and data extraction*

Four reviewers (PW, RH, RAK, AB) screened all titles and abstracts retrieved from the search for studies that met the inclusion criteria. The full manuscripts of studies that potentially met the inclusion criteria were reviewed and the final decision to include or exclude studies was made with two other reviewers (CSK and MAM). Independent double extractions were performed by four reviewers (PW, RH, RAK, AB) and data were collected on study design, year, country, number of women, mean age, parity, cohort characteristics, definition of pre-eclampsia, outcomes assessed, timing of assessment and results.

*Study quality assessment*

We assessed for quality of the studies using the Ottawa Newcastle Scale [15]. Representativeness of the exposed cohort was based on whether the study only evaluated patients of a subgroup of the general population thus limiting generalizability compared to the general female population. Selection of the non-exposed cohort was considered by evaluating whether the reference or comparator group without pre-eclampsia was included based on a specific criteria or were a non-selected group. Ascertainment of exposure was evaluated by considering the likelihood that cases were misclassified as having pre-eclampsia when they did not or cases which were wrongly classified as not having pre-eclampsia. Methods for studies where all patients were assessed for pre-eclampsia were deemed to be more reliable. Studies which excluded patients with baseline diabetes were more reliable in terms of demonstration that outcome of interest was not present at the start of the study. The comparability of the cohort was considered by whether the study had baseline differences between the group with pre-eclampsia and without pre-eclampsia and whether the analysis matched or adjusted for these differences. Higher quality studies either did not have differences in baseline characteristics or used adjustments for differences in baseline characteristics. Assessment of outcome was considered a quality criterion where highest quality is independent blind assessment followed by record linkage. Low quality was where there were self-reported results or no description. Duration of follow-up was another quality indicator where if studies followed up patients for more than 10 years. The final quality assessment area was the adequacy of follow-up, which was deemed to be high if all subjects were accounted for and followed by loss to follow-up <10%. Low quality studies were those with >10% loss to follow-up or if no statement regarding follow-up was provided. We planned to conduct asymmetry testing for publication bias provided that there were >10 studies in the meta-analysis and if statistical heterogeneity was <50% [16].

*Data synthesis and analysis*

We used RevMan Version 5.3.5 (Nordic Cochrane Centre) to conduct random effects meta-analysis using the inverse variance method for pooling log risk ratios (RRs). We used random effects because the studies were conducted in a wide range of settings in different populations, hence the need to take heterogeneity into account for the pooled effect estimate. Where possible, we chose to pool adjusted risk estimates from primary studies and when these data were not available, raw data were used to calculate unadjusted risk estimates. The primary outcome was any diabetes and analysis was performed considering adjusted and unadjusted group separately. Secondary analysis was performed considering the risk of type 1 diabetes and type 2 diabetes separately. Statistical heterogeneity was assessed using the I2 statistic where I2 values of 30-60% represented moderate level of heterogeneity [17]. Where there was moderate or greater degree of heterogeneity, we performed leave-one-out analysis to identify studies which contributed to high degree of heterogeneity. Sensitivity analysis was performed considering the follow-up of the studies for diabetes (<1 year, 1-5 years, 6-10 years and >10 years), exclusion of women with baseline diabetes and hypertension, and baseline differences in BMI, age and gestational diabetes. For the sensitivity analysis on gestational diabetes, in cases where there were more than 2 separate groups being studied, we selected the group with no pre-eclampsia versus the group with pre-eclampsia but no gestational diabetes for data abstraction.

**Results**

*Description of studies included in analysis*

The process of study selection is shown in Figure 1. Out of 10,724 titles and abstracts screened, there were 21 relevant studies with a total of 2,883,658 women (ranged from 140 to 948,035 women in each study). The study design, women’s demographics are shown in Table S1. There were 72,860 women with pre-eclampsia and 1,961,159 women without pre-eclampsia from 20 studies that reported numbers of women in each group. 4 studies were of primiparous women [18-21] and 17 studies were of women with any parity [9-12, 18, 22-33]. The mean age from the women ranged from 23.4 to 31 years at index pregnancy.

*Quality assessment in included studies*

The quality assessment of included studies using the Ottawa Newcastle Scale [15] is shown in Table S2A and S2B.A total of 19 studies were deemed to have reliable methods for ascertainment of pre-eclampsia which included review of medical charts, discharge codes, national databases and other registries [9, 10, 12, 18-26, 28-34] and 18 used reliable methods for ascertainment of diabetes which included blood glucose testing, medical records, direct assessment and use of insurance or registry data [9, 10, 12, 18-28, 30, 32-34]. Loss to follow-up was <10% in 10 studies [9-11, 19, 22, 26, 28, 30, 32, 34]. Adjusted analysis was used in 16 studies [9, 10, 18-25, 27-29, 32-34].

*Determining pre-eclampsia and results of studies*

A variety of different methods were used to ascertain pre-eclampsia. The most common definition used was the International Society of the Studies of Hypertension in Pregnancy (ISSHP) (2014) definition [35]. Follow-up for incident diabetes was up to 46 years. Results are shown in Table S3.

*Pooled analysis of pre-eclampsia and diabetes*

For the future risk of any diabetes (type 1 or type 2) with pre-eclampsia there were 17 studies: 10 of which adjusted for potential confounders [9, 10, 18, 20, 21, 23, 28, 29, 32, 33] (Figure 2A). The confounders that were adjusted for in the analyses are presented in Table S2. The pooled results suggest a significant increase in future incident diabetes risk associated with pre-eclampsia (risk ratio (RR) 2.21, 95% CI 1.86, 2.63, I2=53%) (Figure 2A). The results were also statistically significant for the studies that adjusted for baseline confounders (adjusted risk ratio (aRR) 2.37, 95% CI 1.89, 2.97, I2=67%).

Figure 2B shows the results for the pooled analysis for studies of pre-eclampsia and type 1 and type 2 diabetes. There was only one study of type 1 diabetes which was by Savitz et al. in 2014 [22] where there was no significant association between pre-eclampsia and future incident type 1 diabetes. For incident type 2 diabetes, however, there was a significant increase in risk associated with pre-eclampsia from the 4 pooled studies (RR 2.37, 95% CI 1.37, 4.10, I2=95%) [22, 24, 27, 34].

*Sensitivity analysis for follow-up time and baseline diabetes and hypertension exclusions*

Sensitivity analysis was performed to consider the effect of follow-up time for diabetes and exclusion of baseline diabetes and hypertension (Table 1). There were 3 studies with <1 year follow-up, 2 studies with 1-5 years follow-up, 9 studies with 6-10 years follow-up and 7 studies with >10 years follow-up (Figures S1-4). For any diabetes, the pooled results showed there was a greater risk of any diabetes in women who had pre-eclampsia compared with those who did not have pre-eclampsia when they were followed up from <1 year post-partum and this effect persisted beyond 10 years of follow-up (<1 year: RR 1.97, 95% CI 1.35, 2.87, 1-5 years: RR 2.99, 95% CI 2.44, 3.66, 6-10 years: RR 2.62, 95% CI 1.96, 3.50, and >10 years: RR 1.95, 95% CI 1.28, 2.97). We were able to examine studies for risk of future type 2 diabetes only, this showed that an increased risk of type 2 diabetes is already apparent after a follow-up period <1 year and persisted until 10 years, albeit the numbers of studies were small. We then concentrated on studies that had either excluded baseline diabetes or hypertension from the study cohort. This showed that a significant increased risk in any diabetes remains in the pre-eclampsia group (diabetes exclusion: aRR 2.34, 95% CI 1.86, 2.93 and hypertension exclusion: aRR 2.40, 95% CI 1.97, 2.92, respectively). The individual Forest plots are shown as supplementary figures (Figure S1-S6).

*Sensitivity analysis considering studies that adjusted for BMI, age, and gestational diabetes between pre-eclampsia and control groups*

We conducted sensitivity analysis to consider confounding factors of BMI, age and gestational diabetes (Table 2). We were unable to examine other important confounding factors due to the lack of studies presenting this data. Following adjustment for BMI in pre-eclampsia and control groups, there is a significant increased risk of any diabetes (aRR 2.38, 95% CI 1.74, 3.24) and type 2 diabetes (aRR 2.53, 95% CI 1.64, 3.90). This increased risk remained in studies which also excluded baseline hypertension and diabetes at recruitment (aRR 2.61, 95% CI 1.79, 3.80). In studies that adjusted for age in pre-eclampsia and control groups, there was a statistically significant increased risk of both any diabetes (aRR 2.35, 95% CI 1.87, 2.95) and type 2 diabetes (aRR 2.37, 95% CI 1.37, 4.10). Further sensitivity analysis was performed on studies that have either excluded or adjusted for gestational diabetes. There was a statistically significant increased risk for any diabetes (aRR 2.36, 95% CI 1.94, 2.88). Figures S7-S10 show the individual Forest plots for data presented in Table 2.

The full metabolic risk factor profile of the pre-eclampsia and control population is shown in Table S4. There were significant differences in age, BP and BMI between the pre-eclampsia and control groups at their follow-up in 5 [11, 12, 21, 26, 30], 8 [11, 12, 18, 19, 25, 26, 29, 30] and 6 [11, 12, 19, 21, 26, 30] studies out of 21 studies, respectively. However, this population consists of only 0.5% of total participant women as the metabolic risk factor profile were not available in the studies that contributed to majority of the participants in this systematic review and meta-analysis [10, 22, 28, 34].

**Discussion**

Our systematic review and meta-analysis of 21 studies including over 2.8 million women suggests that there is an association of pre-eclampsia with future incident diabetes. The risk of diabetes is approximately double that of those without a history of pre-eclampsia, and increases to 2.4 fold if type 2 diabetes is considered exclusively. This effect is seen in the first year following delivery and persists beyond 10 years. Diabetes is a well-known risk factor for pre-eclampsia [36]. However, pre-eclampsia has not been established as a risk factor for future diabetes. In comparison, gestational diabetes is a well-recognised risk factor for future diabetes. Women with pregnancies complicated by gestational diabetes have a 7 fold increased risk of developing type 2 diabetes compared with those who had normoglycaemic pregnancies [37]. Our study therefore extends the literature on the association between pre-eclampsia and diabetes.

Current research supports the link between pre-eclampsia and future diabetes with several national or regional registry studies using large sample sizes and adjustment for confounding factors all showing similar results [9, 10, 22, 28, 34]. The studies that have not shown an association are mainly those with smaller sample sizes [11, 12, 18, 19, 21, 23, 25, 26, 29, 30]. There are gaps in the current literature, in particular regarding the link between pre-eclampsia and type 1 diabetes. Furthermore, it is difficult to know whether the association we report relates to confounding factors. We were unable to fully evaluate the effects of all confounding factors and undertake further sensitivity analyses due to the absence of such data in the studies included in the current meta-analysis. For example, only 2 studies adjusted for age and BMI, as well as excluded pre-existing diabetes and hypertension in the study population [22, 32]. Moreover, only 7 studies either adjusted for or excluded patients with gestational diabetes [9, 10, 22, 28, 31-33], a known risk factor for future diabetes and pre-eclampsia development [38]. In the few studies where adjustments for age, BMI or gestational diabetes were made (Table 2), the risk of future type 2 diabetes remains increased in women who had pre-eclampsia compared with the control group.

The underlying mechanism for the association between pre-eclampsia and future diabetes is unclear. Pre-eclampsia and diabetes share common risk factors, i.e. age over 40 years, obesity, hypertension and Afro-Caribbean or South Asian ethnic origin [39, 40]. It may be that women with pre-eclampsia have an underlying predisposition to insulin resistance and metabolic syndrome and present with pre-eclampsia as an early indicator of their adverse metabolic phenotype over the life course.

Risk scores allow a non-invasive method of identifying individuals at high risk of future diabetes. The American Diabetes Association risk tool accounts for age, BMI, hypertension, history of gestational diabetes, family history of diabetes, gender and levels of physical activity [41]. The Finnish Diabetes Risk Score (FINDRISC) [42] is the most commonly used score in Europe, and has been endorsed by the European Society of Cardiology, European Association for the Study of Diabetes [43] and Public Health Agency of Canada [44]. FINDRISC predicts the 10-year risk of developing type 2 diabetes by considering factors on: age, BMI, use of antihypertensive medication, history of hyperglycaemia (including gestational diabetes), family history of diabetes, waist circumference, physical activity and fruit and vegetable intake [42].

Currently, screening beyond history-taking to identify risk factors for pre-eclampsia during pregnancy is not recommended by the American College of Obstetricians and Gynaecologists (ACOG). Recognised risk factors by ACOG are: age older than 40 years, obesity, chronic hypertension, diabetes (type 1 or type 2), chronic renal disease, previous pre-eclampsia, thrombophilia, systemic lupus erythematosus, primiparity, multiple pregnancy, *in vitro* fertilization and family history of pre-eclampsia [45]. This overlap of risk factors for developing pre-eclampsia and type 2 diabetes could have contributed to the association of pre-eclampsia and future diabetes we report here. Furthermore, there is likely to be interplay between the cardiovascular and metabolic systems. A history of pre-eclampsia is also related to poor future cardiovascular health, whilst cardiovascular disease is itself a known risk factor for diabetes [46]. In the few studies where adjustments for age or BMI were made (Table 2), the risk of future type 2 diabetes remains increased in women who had pre-eclampsia compared with the control group. Nevertheless, as highlighted above a number of risk factors are known to significantly increase the risk of future diabetes, and none of the studies included in this meta-analysis fully adjusted for all of these risk factors and so we were unable to undertake further sensitivity analyses.

The strength of our study lies within number of recent studies and the large sample size; our meta-analysis of 21 studies examined over 2.8 million women including over 72,000 pre-eclampsia women with 845,834 patient-years follow-up. The inclusion of more recent studies means that there is a greater likelihood of their findings being generalizable to current practice. The majority of the studies were designed to examine future diabetes or insulin resistance and metabolic syndrome as their main outcome (*n*=18), and contribute to 99% of the women in our meta-analysis.

There are a number of limitations to our analysis. As with any meta-analysis, there is an inherent limitation from publication bias, where studies with positive findings are more likely to be published than one that show neutral outcomes. The majority of the women were from retrospective studies, where there is limited control over quality of data collected. There may be inconsistent, incomplete or inaccurate historical data of pre-eclampsia diagnosis, as well as recall bias, which could have caused incorrect assignment of case and control groups. Five studies used questionnaire data to assess the outcome of diabetes [11, 25, 26, 29, 31]. Finally, it is likely that significant unmeasured confounders may have contributed to our reported association between pre-eclampsia and future diabetes risk, as none of the studies included in this analysis adequately adjusted for all of the risk factors that form the basis of many of the established diabetes risk prediction scores [41, 47].

Given the gaps in the current literature, further work is required to examine the association between pre-eclampsia and type 1 diabetes in particular. There is a need for studies that use propensity matching methods or more comprehensive adjustments for confounding factors, as well as high quality studies with long-term follow-up for outcome events. In addition, mechanistic research is required to further our understanding of the association between pre-eclampsia and future diabetes in order to identify risk reduction strategies.

Our finding of an association between pre-eclampsia and the future development of incident diabetes is clinically important as it suggests that formal risk assessment for the future development of diabetes using established risk scores may be considered in pregnant women with pre-eclampsia [41, 47]. Furthermore, clinicians may find it pertinent to enquire on the history of pre-eclampsia as a part of the metabolic and cardiovascular assessment of women or to incorporate into risk prediction formulae. Since women with pre-eclampsia are already known to be at risk of future cardiovascular diseases [48], our study highlights the importance of lifestyle and risk factor modification, and regular monitoring of BMI and HbA1C in these women to further reduce their cardiovascular and metabolic risks. In line with the ACOG guidance to perform annual fasting glucose testing following severe pre-eclampsia [45], we recommend a detailed cost-benefit analysis to determine whether and when a screening programme for diabetes in this high-risk population should be initiated.

**Conclusion**

Our meta-analysis of 21 studies examined over 72,000 women with pre-eclampsia show that pre-eclampsia is independently associated with a two-fold increase in future diabetes. This increased risk is observed from 1 year following delivery and persists beyond 10 years post-partum. It is likely that significant unmeasured confounders contribute to the association that we have reported, and that a shared adverse risk factor profile may contribute to both pre-eclampsia and future diabetes risk. As women with pre-eclampsia are already known to be at risk of future cardiovascular diseases [48], our study highlights the need for education on risk, advice about the lifestyle modifications required, and regular monitoring of BMI and HbA1C, in women who have had pre-eclampsia. There is a need for evaluation of a screening programme for diabetes in this high-risk population.

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**Legends**

**Figure 1.** Flow diagram of study inclusion.

**Figure 2.** Risk of diabetes with pre-eclampsia. (A) Risk of any diabetes with pre-eclampsia, unadjusted and adjusted. (B) Risk of type 1 diabetes and type 2 diabetes with pre-eclampsia.

**Table 1.** Sensitivity analysis considering follow-up time and exclusions of baseline diabetes or hypertension.

|  |  |  |  |
| --- | --- | --- | --- |
| **Sensitivity analysis** | **PE and risk of outcome** | **Number of studies** | **Risk ratio (95% CI)** |
| **Time period of follow-up** | | | |
| Studies with follow-up <1 year | Adjusted risk of any DM | 2 | 2.17 (0.71, 6.54) |
| Type 1 DM | 1\* | 1.80 (0.83, 3.92) |
| Type 2 DM | 1\* | 2.00 (1.25, 3.20) |
| Pooled analysis | 3 | 1.97 (1.35, 2.87) |
| Studies with follow-up 1-5 years | Unadjusted risk of any DM | 1 | 1.32 (0.05, 31.83) |
| Adjusted risk of any DM | 1 | 3.00 (2.45, 3.67) |
| Pooled analysis | 2 | 2.99 (2.44, 3.66) |
| Studies with follow-up 6-10 years | Unadjusted risk of any DM | 3 | 7.42 (1.30, 42.30) |
| Adjusted risk of any DM | 5 | 2.43 (1.72, 3.44) |
| Type 2 DM | 1 | 3.11 (2.10, 4.61) |
| Pooled analysis | 9 | 2.62 (1.96, 3.50) |
| Studies with follow-up >10 years | Unadjusted risk of any DM | 3 | 1.80 (1.35, 2.42) |
| Adjusted risk of any DM | 2 | 1.94 (1.00, 3.77) |
| Type 2 DM | 2 | 2.25 (0.90, 5.61) |
| Pooled analysis | 7 | 1.95 (1.28, 2.97) |
| **Exclusion of baseline comorbidity** | | | |
| Studies which excluded baseline DM | Unadjusted risk of any DM | 5 | 2.14 (1.62, 2.82) |
| Adjusted risk of any DM | 7 | 2.41 (1.88, 3.09) |
| Type 1 DM | 1\* | 1.80 (0.83, 3.92) |
| Type 2 DM | 3\* | 2.17 (1.08, 4.37) |
| Pooled analysis | 15 | 2.34 (1.86, 2.93) |
| Studies which excluded baseline hypertension | Unadjusted risk of any DM | 2 | 1.97 (0.22, 17.82) |
| Adjusted risk of any DM | 6 | 2.55 (1.98, 3.27) |
| Type 1 DM | 1\* | 1.80 (0.83, 3.92) |
| Type 2 DM | 1\* | 2.00 (1.27, 3.14) |
| Pooled analysis | 9 | 2.40 (1.97, 2.92) |

CI=confidence interval, DM=diabetes mellitus, PE=pre-eclampsia. \*The same study with subgroups of type 1 DM and type 2 DM.

**Table 2.** Sensitivity analysis considering risk of pre-eclampsia and diabetes in studies which adjusted for BMI, BMI with exclusion of baseline hypertension and diabetes, age, and gestational diabetes.

|  |  |  |
| --- | --- | --- |
| **Adjustment for BMI** | Studies | Risk Ratio (95% CI) |
| Any DM | 4 | 2.41 (1.37, 4.24) |
| T1DM | 1\* | 1.80 (0.83, 3.92) |
| T2DM | 2\* | 2.53 (1.64, 3.90) |
| Pooled analysis | 6 | 2.38 (1.74, 3.24) |
| **Adjustment for BMI excluding baseline HTN and DM** | | |
| Any DM | 2 | 3.48 (2.37, 5.10) |
| T1DM | 1\* | 1.80 (0.83, 3.92) |
| T2DM | 1\* | 2.00 (1.27, 3.14) |
| Pooled analysis | 3 | 2.61 (1.79, 3.80) |
| **Adjustment for age** | | |
| Any DM, matched | 2 | 6.07 (0.72, 51.38) |
| Any DM, adjusted | 8 | 2.32 (1.86, 2.91) |
| T1DM, adjusted | 1\* | 1.80 (0.83, 3.92) |
| T2DM, adjusted | 4\* | 2.37 (1.37, 4.10) |
| Pooled analysis | 14 | 2.35 (1.87, 2.95) |
| **Adjustment for gestational diabetes** | | |
| Any DM, excluded GDM, unadjusted | 1 | 2.08 (1.57, 2.75) |
| Any DM, excluded GDM, adjusted | 4 | 2.96 (2.04, 4.29) |
| Any DM, adjusted for GDM | 1 | 1.82 (1.26, 2.62) |
| T1DM, adjusted for GDM | 1\* | 1.80 (0.85, 3.80) |
| T2DM, adjusted for GDM | 1\* | 2.00 (1.25, 3.20) |
| Pooled analysis | 7 | 2.36 (1.94, 2.88) |

BMI=body mass index, CI=confidence interval, DM=diabetes mellitus, GDM=gestational diabetes, HTN=hypertension, PE=pre-eclampsia. \*The same study with subgroups of type 1 DM and type 2 DM.

**Table S1.** Study design and participant characteristics.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Study ID** | **Study Design; Country; Year** | **Total No. of Women (PE/no PE)** | **Mean Age** | **Parity** | **Participant Selection Criteria** | **Outcomes Assessed** |
| Andersgaard et al (2012) [11] | Cross-sectional study; Norway; 1994-1995. | 8,088 (PE 901, control 7,187) | 23.4\* | A | Women in the Tromso study which focuses on cardiovascular risk factors. | Any diabetes or use of antidiabetic medication, self-reporting on questionnaire. |
| Callaway et al (2007) [31] | Prospective cohort study; Australia, 1981-1984 | 3,639 (PE 333, control 3,306) | 25\* | A | Women in the Mater-University of Queensland Study of Pregnancy between 1981-1984. | Any diabetes, self-reporting on questionnaire. |
| Libby et al (2007) [24] | Prospective cohort study; Scotland; 1952-2003. | 7,187 (PE 810, control 6,377) | Median of 25 and 26\* | A | Women in the Walker Database, which included the majority of women delivering in Dundee between 1952-1966. | Type 2 diabetes, confirmed by manual validation of case records. |
| Kaaja et al (2005) [26] | Retrospective cross-sectional study; Finland; 2002. | 3559 (PE 397, control 3,162) | 26.7\* | A | Women in FINRISK-cross sectional survey which monitors cardiovascular risk factors in Finland every 5 years. | Any diabetes, self-reporting on questionnaire. |
| Mannisto et al (2013) [23] | Prospective cohort study; Finland; 1966-2006. | 6,794 (PE 242, control 6,552) | 26.7\* | A | Women in the prospective Northern Finland Birth Cohort 1966, which composed of all expected births in 1966. | Any diabetes, ascertained by ICD codes. |
| Lykke et al (2009) [34] | Retrospective cohort study; Denmark; 1978-2007. | 774,838 (PE 33,826, control 741,012) | 26.8\* | P | Women age 15-50 who had first delivery from 1978-2007 in the National Patient Registry in Denmark. | Type 2 diabetes, obtained from the National Patient Registry in Denmark. |
| Forest et al (2005) [19] | Prospective case-control study; Canada; 1989-1997. | 231 (PE 63, control 168) | 27.2\* | P | Women in previous prospective studies for biochemical and sonographic markers of PE and matched controls. | Fasting blood glucose ≥7mmol/l, blood sampled in research clinic. |
| Edlow et al (2009) [29] | Prospective case-control study; USA; 2005-2007. | 219 (PE 79, control 140) | 27.5\* | A | Women in the Pre-eclampsia: Mechanisms and Consequences study from Hospital of the University of Pennsylvania between March 2005-August 2007. | Any diabetes, assessed through telephone questionnaire. |
| Berends et al (2008) [30] | Case-control study; Netherlands; 1983-2004. | 153 (PE 47, control 106) | 27.7\* | A | Women with a history of PE recruited from the Genetic Research in Isolated Populations Study. | Any diabetes, participants examined at research centre. |
| Wang et al (2012) [32] | Retrospective cohort study; Taiwan; 1997-2008 | 5,178 (PE 651, control 4,527). | 29\* | A | Random subset from National Health Insurance Research Database 1997-2003. | Any diabetes, ascertained by ICD-9. |
| Drost et al (2012) [18] | Retrospective cohort study; Netherlands; 1991-2007. | 671 (PE 339, control 332) | 29.2\* | A | Women delivered at the Isala Klinieken in Zwolle, The Netherlands between 1991-2007 with and without PE. | Any diabetes, ascertained by trained nurses at cardiology clinic. |
| Van Rijn et al (2013) [21] | Prospective cross-sectional study; Netherlands; 1994-2007. | 617 (PE 243, control 374) | 29.4\* | P | Women with a first pregnancy complicated by early onset PE in a tertiary centre in the Netherlands, versus the control group from a study that comprises an unselected population-based cohort of similar age, demographics, and geographical background. | Any diabetes, assessed in research clinic. |
| Feig et al (2013) [10] | Retrospective cohort study; Canada; 1994-2008. | 948,035 (PE 22,933, control 925,102) | 29.5\* | A | Linkage of administrative health claims for public health insurance with the Canadian Institute for Health Information Discharge Abstract Database for delivery information. | Any diabetes, through health insurance claims. |
| Carr et al (2009) [9] | Retrospective cohort study; USA; 1985-2002. | 31,463 (PE 2,032, control 29,431) | 30.1\* | A | Women with and without PE in Group Health, a Washington state health plan, linked to subsequent automated data for the diagnosis of diabetes (using ICD-9 codes). | Any diabetes, via ICD-9 codes, laboratory and pharmacy records. |
| Lazdam et al (2012) [25] | Prospective cohort study; England; 1998-2003. | 140 (PE 90, control 50) | 30.4\* | A | Women who were discharged from Oxford Maternity Unit between 1998-2003. | Any diabetes, self-reporting on questionnaire. |
| Engeland et al (2011) [28] | Prospective cohort study; Norway; 2004-2008. | 226,832 (PE 8,822, control 218,010) | 31\* | A | Women with pregnancies registered in the Medical Birth Registry of Norway during 2004–2008. | Use of antidiabetic medication, using national prescription data from pharmacies. |
| Breetveld et al (2014) [12] | Retrospective cohort study; Netherlands; 2010-2012. | 165 (PE 115; control 50) | 37.5\*\* | A | Recruitment from a database of women who had PE and volunteered to participate in a cardiovascular follow-up study program. | Any diabetes, determined by researcher. |
| Magnussen et al (2009) [20] | Prospective cohort study; Norway; 1967-1995. | 15,065 (PE 661, control 14,404) | 40\*\* | P | Women in the Nord-Trondelag Health (HUNT) study who had first singleton pregnancies from 1976-1995. | Any diabetes, self-reporting on questionnaire then validated by fasting blood glucose. |
| Hashemi et al (2012) [27] | Prospective cohort study; Iran; unclear. | 452 (PE 226, control 226) | Unclear | A | Women in the Tehran Lipid Glucose Study which is on disease risk factors. | Type 2 diabetes, confirmed by oral glucose tolerance test. |
| Savitz et al (2014) [22] | Retrospective cohort study; USA; 1995-2004. | 849,639 (no data on numbers in the PE cohort) | Unclear | A | Data on all births in hospitals in New York City obtained by linking birth certificates to hospital discharge data. | Type 1 and type 2 diabetes, ascertained by ICD-9 codes. |
| Tam et al (2015) [33] | Case-control study; Hong Kong; unclear. | 693 (PE 50, controls 643) | Unclear | A | Women in the Hyperglycemia and Adverse Pregnancy Outcome study, a multinational study. | Any diabetes, assessed by oral glucose tolerance test. |

A=any parity, HTN=hypertension, P=primiparous, PE=pre-eclampsia. \* At index pregnancy. \*\* At follow-up.

**Table S2A.** Study quality assessment overview.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study ID** | **Selection** | | | | **Comparability** | **Outcome** | | | **Total Score** |
| **Representative of the exposed cohort** | **Selection of the non-exposed cohort** | **Ascertainment of exposure** | **Demonstration that outcome of interest was not present at start of study** | **Comparability of cohort** | **Assessment of outcome** | **Follow-up duration to capture outcomes** | **Adequacy of follow-up** |
| Andersgaard et al (2012) [11] | \* | \* |  |  |  |  | \* | \* | 4 |
| Callaway et al (2007) [31] | \* | \* | \* | \* |  |  | \* |  | 5 |
| Libby et al (2007) [24] | \* | \* | \* | \* | \* | \* | \* |  | 7 |
| Kaaja et al (2005) [26] | \* | \* | \* |  |  | \* | \* | \* | 6 |
| Mannisto et al (2013) [23] | \* | \* | \* | \* | \*\* | \* | \* |  | 8 |
| Lykke et al (2009) [34] | \* | \* | \* | \* | \* | \* | \* | \* | 8 |
| Forest et al (2005) [19] | \* | \* | \* | \* | \* | \* |  | \* | 7 |
| Edlow et al (2009) [29] | \* | \* | \* |  | \* |  |  |  | 4 |
| Berends et al (2008) [30] | \* | \* | \* | \* |  | \* |  | \* | 6 |
| Wang et al (2012) [32] | \* | \* | \* | \* | \*\* | \* |  | \* | 8 |
| Drost et al (2012) [18] | \* |  | \* |  | \* | \* | \* |  | 5 |
| Van Rijn et al (2013) [21] | \* |  | \* |  | \* | \* |  |  | 4 |
| Feig et al (2013) [10] | \* | \* | \* | \* | \* | \* |  | \* | 7 |
| Carr et al (2009) [9] | \* | \* | \* | \* | \*\* | \* |  | \* | 8 |
| Lazdam et al (2012) [25] | \* |  | \* | \* | \* | \* | \* |  | 6 |
| Engeland et al (2011) [28] | \* | \* | \* | \* | \* | \* |  | \* | 7 |
| Breetveld et al (2014) [12] | \* | \* | \* | \* |  | \* |  |  | 5 |
| Magnussen et al (2009) [20] | \* | \* | \* | \* | \* | \* | \* |  | 7 |
| Hashemi et al (2012) [27] | \* |  |  |  | \* | \* | \* |  | 4 |
| Savitz et al (2014) [22] | \* | \* | \* | \* | \*\* | \* |  | \* | 8 |
| Tam et al (2015) [33] | \* | \* | \* | \* | \* | \* | \* |  | 7 |

**Table S2B.** Study quality assessment in detail.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study ID** | **Representative of the exposed cohort** | **Selection of the non-exposed cohort** | **Ascertainment of exposure** | **Demonstration that outcome of interest was not present at start of study** | **Comparability of cohort** | **Assessment of outcome** | **Follow-up duration to capture outcomes** | **Adequacy of follow-up** |
| Andersgaard et al (2012) [11] | General cohort of women. | Controls from same cohort. | Completed questionnaires. | No exclusions. | Unadjusted | Self-reported diabetes or use of antidiabetic medication. | Mean 24.7 years. | 434/10,408 (4%) loss to follow-up. |
| Callaway et al (2007) [31] | General cohort of women. | Controls from the same cohort. | Identified from previous study. | Excluded diabetes and gestational diabetes. | Unadjusted. | Self-reported diabetes. | 21 years. | 3,639/7,173 (51%) did not complete questionnaire. |
| Libby et al (2007) [24] | General cohort of women. | Controls from same cohort. | From database. | Excluded type 1 diabetes. | Adjusted for age, socioeconomic status, birthweight of the offspring. | From use of medicines database (1980-1993) and the diabetic database on all diabetics in the area (from 1993). | Median 46 years. | 1,192/8,384 (14%) had died or moved from study area. |
| Kaaja et al (2005) [26] | General cohort of women. | Controls from same cohort. | Completed questionnaires with trained staff. | No exclusions. | Unadjusted | Completed questionnaire with trained staff. | Mean 17.4 years. | >90% came for the assessments with trained staff at their local health care centre. |
| Mannisto et al (2013) [23] | General cohort of women. | Controls from same cohort. | Medical records reviewed by 2 obstetricians. | Excluded diabetes. | Adjusted for BMI, smoking parity and socioeconomic status. | ICD codes recorded in Finnish registers. | Mean 39.4 years. | 1,565/12,055 (13%) had missing blood pressures or died. |
| Lykke et al (2009) [34] | General cohort of women. | Controls from same cohort. | Data from national database. | Excluded diabetes. | Adjusted for age, year of delivery, preterm delivery, placental abruption, small-for-gestational-age offspring and stillbirth. | From the National Patient Registry in Denmark. | Median 14.6 years. | 24,778/807,065 (3%) died or emigrated. |
| Forest et al (2005) [19] | General cohort of primiparous women. | Matched controls for maternal age and year of index delivery from same cohort. | PE assessed by 1 senior obstetrician. | Excluded diabetes. | Unadjusted, but matched for age. | Assessed at research clinics run by research nurses. | Mean 7.8 years. | No loss to follow-up. |
| Edlow et al (2009) [29] | General cohort of women with diagnosis of PE. | General cohort of women without diagnosis of PE. | Women identified from previous study. | No exclusions. | Adjusted for ethnicity, BMI, parity. | Assessed through a telephone questionnaire. | 6-13 months after delivery. | Out of eligible patients, participated by PE 79 /113 (70%) and control 140/239 (59%) women. |
| Berends et al (2008) [30] | General cohort of women from the Genetic Research in Isolated Populations study, where all participants were of White origin. | Controls from the Erasmus Rucpphen Family study, a substudy of the Genetic Research in Isolated Populations study | A research physician reviewed the medical charts. | Excluded diabetes. | Unadjusted. | All participants were examined at research centre. | Median 7.1 years. | Participated by 153/156 (98%), exclusion due to pregnancy. |
| Wang et al (2012) [32] | General cohort of women. | Matched by age and year of pregnancy from the same cohort. | From database. | Excluded diabetes and gestational diabetes. | Adjusted for age, occupation, obesity and hyperlipidemia. | Identified using ICD-9 codes. | Mean 8.2 years. | Database study. |
| Drost et al (2012) [18] | General cohort of women. | Age matched controls. | Database to identify women with PE. | No exclusions. | Adjusted for age, years post-index pregnancy and current smoking. | Ascertained by trained nurses. | Mean 10.0 years. | Out of eligible participants, participated by PE 339/448 (76%) and control 332/617 (54%) women. |
| Van Rijn et al (2013) [21] | General cohort of primiparous women. | Similar age controls. | Women identified from previous studies. | No exclusions. | Adjusted for age and oral contraceptive use. | Assessed at research clinic. | Mean 9.4 months. | Unclear. |
| Feig et al (2013) [10] | General cohort of women. | Controls from same cohort. | Data from national database. | Excluded diabetes and gestational diabetes. | Adjusted for age, socioeconomic status, hypertension prior to pregnancy, and comorbidity. | Identified through health insurance claims. | Median 8.5 years. | Database study. |
| Carr et al (2009) [9] | General cohort of women. | Controls from same cohort. | From discharge codes. | Excluded diabetes. | Adjusted for age, primigravidity and gestational diabetes. | Used ICD-9 codes, laboratory and pharmacy records. | Median 8.2 years. | Database study. |
| Lazdam et al (2012) [25] | General cohort of women. | Match for age, parity, and year of delivery.. | Extracted from medical records. | Excluded diabetes. | Unadjusted but matched for age and parity. | Completed questionnaire with research midwife. | 9.75 years. | Out of eligible participants, 140/618 (23%) participated. |
| Engeland et al (2011) [28] | General cohort of women. | Controls from same cohort. | Data from national database. | Excluded diabetes and gestational diabetes. | Adjusted for age and parity. | Use of national prescription data from pharmacies to identify those newly started on antidiabetic medication. Medication dispensed at hospitals were not included. | Mean 3.7 years. | Database study. |
| Breetveld et al (2014) [12] | General cohort of women. | Women in control group had to be between 25 and 45 years old and to have had their first pregnancy 5-10 years earlier. | Women identified from previous study. | Excluded diabetes. | Unadjusted. | Assessed at research facility. | Mean 5.4 years (PE) and 8.0 years (control). | Unclear. |
| Magnussen et al (2009) [20] | General cohort of women. | Controls from same cohort. | Data from national database. | Excluded diabetes. | Adjusted for age, duration between index delivery and HUNT study, education, smoking, BMI, and whether receiving social security benefit. | Fasting blood glucose taken to confirm diabetes. | Mean 16.5 years. | Unclear. |
| Hashemi et al (2012) [27] | General cohort of women. | Age and BMI matched controls. | Completed questionnaires. | No exclusions. | Unadjusted but matched for age and BMI. | Oral glucose tolerance test. | 10 years. | Unclear. |
| Savitz et al (2014) [22] | General cohort of women. | Controls from same cohort. | Use of hospital discharge information. | Excluded diabetes. | Adjusted for year, age, ethnicity, health insurance, gestational diabetes, parity, socioeconomic status, smoking, prenatal care and pre-pregnancy weight. | Identified using ICD-9 codes. | Within 1 year. | Database study. |
| Tam et al (2015) [33] | General cohort of women | Controls from same cohort. | Identified from previous study. | Excluded diabetes and gestational diabetes. | Adjusted for unclear variables. | Oral glucose tolerance test. | 7-11 years. | Unclear. |

BMI=body mass index, PE=pre-eclampsia

**Table S3.** Method of determining pre-eclampsia, outcomes and results

|  |  |  |  |
| --- | --- | --- | --- |
| **Study ID** | **Definition of PE** | **Timing of outcome assessment** | **Results** |
| Andersgaard et al (2012) [11] | Self-reported gestational hypertension and proteinuria. | Mean 24.7 years follow-up. | PE vs control: DM 17/901 vs 107/7,187 . |
| Callaway et al (2007) [31] | Diastolic BP >90 mmHg on 2 occasions associated with proteinuria or excessive fluid retention after 20 weeks gestation. | 21 years follow-up. | PE vs control: DM: 51/333 vs 244/3,306. |
| Libby et al (2007) [24] | Diastolic BP ≥90 mmHg on ≥2 occasions separated by 1 day and albuminuria. | Median 46 years follow-up. | PE vs control: Type 2 DM: 107/810 vs 703/6,377, aOR 1.40 (1.12-1.75). |
| Kaaja et al (2005) [26] | ISSHP (2014) definition. | Mean 17.4 years follow-up. | PE vs control: DM: 13/397 vs 54/3,162 |
| Mannisto et al (2013) [23] | ≥145/95 mmHg with proteinuria ≥0.3 g/l after 20 weeks gestation.. | Mean 39.4 years follow-up. | PE vs control: DM: 22/242 vs 388/6,552, HR 1.42 (0.92-2.19). |
| Lykke et al (2009) [34] | ISSHP (2014) definition. | Median 14.6 years follow-up. | PE vs control: Type 2 DM: Mild PE: 742/26,810 vs 5,604/741,012, aHR 3.53 (3.23-3.85). Severe PE: 177/7,016 vs 5,604/741,012, aHR 3.68 (3.04-4.46). |
| Forest et al (2005) [19] | ISSHP (2014) definition. | Mean 7.8 years follow-up. | PE vs control: DM: 2/63 vs 0/168. |
| Edlow et al (2009) [29] | BP ≥140/90 mmHg on 2 occasions ≥6 hours apart or BP ≥160/105, with or without proteinuria. | 6-13 months after delivery. | PE vs control: DM: 6/79 vs 5/140, aOR 1.84 (0.5-6.5). |
| Berends et al (2008) [30] | ISSHP (2014) definition. | Median 7.1 years follow-up. | PE vs control : DM: 2/47 vs 0/106. |
| Wang et al (2012) [32] | PE defined by ICD-9 codes. | Mean 8.2 years follow-up. | PE vs control: DM: 31/651 vs 31/4,527, aHR 4.15 (2.48-6.95). |
| Drost et al (2012) [18] | ISSHP (2014) definition. | Mean 10.0 years follow-up. | PE (n=339) vs control (n=332): DM: aOR 1.72 (0.54-5.48). |
| Van Rijn et al (2013) [21] | ISSHP (2014) definition and required delivery <34 weeks gestation. | Mean 9.4 months follow-up. | PE vs control: DM: 3/243 vs 2/374, aOR 3.67 (0.38-35.64). |
| Feig et al (2013) [10] | From hospitalization records and outpatient data from physicians’ services claims. | Median 8.5 years follow-up. | PE vs control: DM: 1,510/22,933 vs 23,108/925,102, aHR 2.08 (1.97-2.19). |
| Carr et al (2009) [9] | PE defined by ICD-9 codes. | Median 8.2 years follow-up. | PE (n=2,032) vs control (n=29,431): DM: aHR 1.82 (1.26-2.62). |
| Lazdam et al (2012) [25] | ISSHP (2014) definition. | Mean 9.75 years follow-up. | PE vs control: DM: 2/90 vs 0/50. |
| Engeland et al (2011) [28] | ISSHP (2014) definition. | Mean 3.7 years follow-up. | PE (n=8,822) vs control (n=218,010): Drugs to treat DM: aRR 3.0 (2.4-3.6). Both insulin and oral antidiabetics: aRR 4.2 (1.6-11). Oral antidiabetics: aRR 3.0 (2.4-3.7). Insulin only: aRR 2.5 (1.4-4.5). |
| Breetveld et al (2014) [12] | ISSHP (2014) definition. | Mean 5.4 years (PE) and 8.0 years (control) follow-up. | PE vs control: DM 1/115 vs 0/50. |
| Magnussen et al (2009) [20] | ISSHP (2014) definition. | Mean 16.3 years (PE) and 16.6 years (control) follow-up. | PE (n=661) vs control (n=14,404): DM: aOR 2.8 (1.6-5.0). |
| Hashemi et al (2012) [27] | ISSHP (2014) definition. | 10 years follow-up. | PE vs control: Type 2 DM: 84/226 vs 27/226. |
| Savitz et al (2014) [22] | PE defined by ICD-9 codes. | Within 1 year follow-up. | PE vs control: Type 1 DM (n=71): aOR 1.8 (0.8-3.8). Type 2 DM (n=212): aOR 2.0 (1.3-3.2). |
| Tam et al (2015) [33] | PE not defined. | 7-11 years follow-up. | PE vs controls: DM: 6/50 vs 3/643, aOR 13.0 (1.9-81.0). |

DM=diabetes mellitus, ISSHP=International Society for the Study of Hypertension in Pregnancy, HTN=hypertension, PE=pre-eclampsia

**Table S4.** Metabolic risk factor profile of PE and control groups in the included studies. \* Total PE vs. control.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Study ID** | **Risk factor profile** | **During pregnancy** | | | **At follow-up** | | |
| **PE** | **Control** | ***p* value** | **PE** | **Control** | ***p* value** |
| Andersgaard 2012 | Age (year) | - | - | - | 48.8 | 47.4 | <0.01 |
| MAP (mmHg) | - | - | - | 100 | 94 | <0.01 |
| BMI (kg/m2) | - | - | - | 26 | 25 | <0.001 |
| Waist circumference (cm) | - | - | - | 87 | 84 | <0.001 |
| Total cholesterol (mmol/l) | - | - | - | 6.12 | 6.04 | <0.05 |
| HDL (mmol/l) | - | - | - | 1.61 | 1.65 | <0.01 |
| Triacylglycerol (mmol/l) | - | - | - | 1.43 | 1.46 | <0.001 |
| HTN >140/90 (%) | - | - | - | 25 | 13 | <0.001 |
| Angina/MI/stroke (%) | - | - | - | 7.7 | 4.2 | <0.001 |
| BMI>30 (%) | - | - | - | 17 | 10 | N.S |
| Smoking (%) | - | - | - | 32 | 38 | N.S |
| FH first degree CVD (%) | - | - | - | 64.9 | 54.8 | N.S |
| FH first degree DM (%) | - | - | - | 19.2 | 16.2 | N.S |
| Callaway 2007 | Not available | - | - | - | - | - | - |
| Libby 2007 | Age (year) | 25 | 26 | N.S | 71 | 71 | N.S |
| Kaaja 2005 | Age (year) | - | - | - | 47.9 | 46.4 | 0.006 |
| HTN in last 12 months | - | - | - | 31.8 | 12.4 | <0.001 |
| HTN ever | - | - | - | 73.8 | 32.7 | <0.001 |
| Antihypertensives, ever used (%) | - | - | - | 52.9 | 29.2 | <0.001 |
| BMI (Kg/m2) | - | - | - | 27.7 | 26.2 | <0.001 |
| Alcohol (g/previous week) | - | - | - | 30.8 | 37.5 | 0.027 |
| Increased cholesterol, ever (%) | - | - | - | 39.0 | 31.4 | 0.006 |
| Angina in last 12 months | - | - | - | 2.5 | 0.8 | <0.001 |
| Cardiac insufficiency in last 12 months (%) | - | - | - | 2.9 | 0.7 | <0.001 |
| Smoking (%) | - | - | - | 21.5 | 22.5 | N.S |
| Cancer (%) | - | - | - | 0.8 | 0.7 | N.S |
| Cholesterol (mmol/l) | - | - | - | 5.4 | 5.4 | N.S |
| Use of lipid-lowering medication (%) | - | - | - | 3.5 | 2.4 | N.S |
| Mannisto 2013 | BMI (Kg/m2) | 23.5 | 22.6 | <0.0001 | - | - | - |
| Primiparous (%) | 55.0 | 30.9 | <0.0001 | - | - | - |
| Smoking (%) | 18.2 | 23.8 | <0.05 | - | - | - |
| Age (%) | 26.7 | 26.6 | N.S | - | - | - |
| Socioeconomic status, managerial (%) | 15.3 | 13.4 | N.S | - | - | - |
| Lykke 2009 | Not available | - | - | - | - | - | - |
| Forest 2005 | Age (year) | 27.4 | 27.0 | N.S | 35.5 | 35.1 | N.S |
| BMI (Kg/m2) | 23.3 | 21.9 | 0.008 | 26.9 | 24.7 | 0.002 |
| SBP (mmHg) | - | - | - | 114.8 | 107.9 | <0.001 |
| DBP (mmHg) | - | - | - | 75 | 70 | <0.001 |
| Waist circumference (cm) | - | - | - | 82.5 | 76.9 | <0.001 |
| Waist/Hip ratio | - | - | - | 0.79 | 0.77 | 0.03 |
| LDL (mmol/l) | - | - | - | 2.90 | 2.65 | 0.05 |
| Apolipoprotein B (g/l) | - | - | - | 0.87 | 0.79 | 0.02 |
| Atherogenic index | - | - | - | 3.8 | 3.4 | 0.03 |
| FH HTN (%) | - | - | - | 65 | 32 | <0.001 |
| Total cholesterol (mmol/l) | - | - | - | 4.77 | 4.54 | N.S |
| HDL (mmol/l) | - | - | - | 1.33 | 1.42 | N.S |
| Triacylglycerol (mmol/l) | - | - | - | 1.18 | 1.02 | N.S |
| Smoking (%) | - | - | - | 24 | 31 | N.S |
| Alcohol (%) | - | - | - | 3 | 5 | N.S |
| Exercise (%) | - | - | - | 17 | 33 | N.S |
| Oral contraceptive use (%) | - | - | - | 18 | 20 | N.S |
| FH of CVD <55 years old (%) | - | - | - | 27 | 17 | N.S |
| FH of DM (%) | - | - | - | 18 | 21 | N.S |
| Edlow 2009 | Chronic hypertension (%) | 15.2 | 5.7 | 0.01 | - | - | - |
| African American (%) | 77 | 60.7 | 0.02 | - | - | - |
| History of PE >1 pregnancy (%) | 20.3 | 5.7 | 0.02 | - | - | - |
| Mean age (year) | 26.6 | 28.3 | N.S | - | - | -- |
| Mean BMI (%) | 29.3 | 29.3 | N.S | - | - | - |
| Smoking (%) | 8.8 | 14.3 | N.S | - | - | - |
| Primiparous (%) | 54 | 42 | N.S | - | - | - |
| HTN/antihypertensive use excluding chronic hypertensives (%) | - | - | - | 38.7 | 4.4 | <0.001 |
| BMI >30 (%) | - | - | - | 48.7 | 29.3 | N.S |
| Dyslipidaemia/lipid-lowering medicine use (%) | - | - | - | 8.0 | 3.1 | N.S |
| Berends 2008 | Age (year) | 29.2 | 26.2 | <0.001 | 36.2 | 39.2 | <0.01 |
| Antihypertensives (%) |  |  |  | 19.1 | 0.9 | <0.001 |
| Median BMI (kg/m2) | - | - | - | 27.2 | 24.2 | <0.01 |
| Low educational level (%) | - | - | - | 38.0 | 72.6 | <0.001 |
| Smoking (%) | - | - | - | 22.0 | 49.1 | <0.001 |
| Lipid-lowering drugs (%) | - | - | - | 2.1 | 0.9 | N.S |
| Alcohol consumption (%) | - | - | - | 32.0 | 31.1 | N.S |
| Wang 2012 | Not available | - | - | - | - | - | - |
| Drost 2012 | Age (year) | 29.8 | 28.6 | <0.05 | - | - | - |
| Primiparous (%) | 79.6 | 70.2 | <0.05 | - | - | - |
| Smoking (%) | 11.2 | 16.6 | N.S | - | - | - |
| HTN (%) | - | - | - | 43.1 | 17.2 | <0.05 |
| FH of cardiovascular risk (%) | - | - | - | 75.5 | 63.9 | <0.05 |
| Antihypertensives (%) | - | - | - | 20.6 | 2.1 | <0.05 |
| Current smoking (%) | - | - | - | 15.6 | 17.5 | N.S |
| Previous smoking (%) | - | - | - | 29.5 | 30.4 | N.S |
| Adequate control of BP on medication (%) | - | - | - | 38.6 | 14.3 | N.S |
| Hypercholesterolaemia (%) | - | - | - | 38.6 | 42.5 | N.S |
| Statin use (%) | - | - | - | 1.2 | 0.3 | N.S |
| Van Rijn 2013 | Age (year) | - | - | - | 30.5 | 28.3 | <0.001 |
| SBP (mmHg) | - | - | - | 126 | 120 | <0.001 |
| DBP (mmHg) | - | - | - | 79 | 70 | <0.001 |
| BMI (Kg/m2) | - | - | - | 26.1 | 24.3 | <0.001 |
| Total cholesterol (mg/dl) | - | - | - | 198 | 186 | <0.001 |
| HDL cholesterol (mg/dl) | - | - | - | 55 | 61 | <0.001 |
| LDL cholesterol (mg/dl) | - | - | - | 119 | 104 | <0.001 |
| Triacylglycerol (mg/dl) | - | - | - | 121 | 108 | 0.009 |
| Ratio of total cholesterol to HDL cholesterol | - | - | - | 3.81 | 3.21 | <0.001 |
| Current oral contraceptive use (%) | - | - | - | 82 | 34 | <0.001 |
| White race (%) | - | - | - | 99 | 98 | N.S |
| Smoking (%) | - | - | - | 25.1 | 27.2 | N.S |
| Feig 2013 | Age (year) | 29.51 | 29.54 | N/A | - | - | - |
| Prior HTN (%) | 6.4 | 1.3 | N/A | - | - | - |
| Chronic medical unstable comorbidity (%) | 12.4 | 10.2 | N/A | - | - | - |
| Chronic medical stable comorbidity (%) | 27.1 | 22.2 | N/A | - | - | - |
| Income quartile 1 (lowest) (%) | 21.4 | 21.8 | N/A | - | - | - |
| Carr 2009 | Gestational DM (%) | 5.7 | 4.2 | N/A | - | - | - |
| Mean age at delivery (year) | 30.0 | 30.1 | N/A | - | - | - |
| Lazdam 2012 | Age (year) | E 39.78 | 30.12 | N.S | E 39.78 | 40.51 | N.S |
| L 30.04 | - | N.S | L 40.04 | - | - |
| Primiparous (%) | E 80 | 80 | N.S | - | - | - |
| L 82 | - | N.S | - | - | - |
| HTN (%) | - | - | - | E 6 | 0 | 0.03\* |
| - | - | - | L 2 |  |  |
| LDL (mmol/l) | - | - | - | E 2.89 | 2.61 | 0.04\* |
| - | - | - | L 2.96 | - | - |
| Total:HDL cholesterol ratio | - | - | - | E 3.53 | 2.95 | 0.002\* |
| - | - | -- | L 3.30 | - | - |
| Triacylglycerol (mmol/l) | - | - | - | E 1.19 | 0.9 | 0.05\*\* |
| - | - | - | L 1.02 | - | - |
| HOMA-IR | - | - | - | E 2.08 | 1.52 | 0.01\* |
| - | - | - | L 2.01 | - | - |
| Smoking (%) | - | - | - | E 12.5 | 4.2 | N.S |
|  |  |  | L 2.3 | - | - |
| Engeland 2011 | Not available | - | - | - | - | - | - |
| Breetveld 2014 | Age (year) | - | - | - | 36 | 39 | <0.001 |
| SBP (mmHg) | - | - | - | 117 | 110 | <0.01 |
| MAP (mmHg) | - | - | - | 86 | 82 | <0.01 |
| BMI >30 (%) | - | - | - | 18 | 4 | <0.05 |
| Alcohol (%) | - | - | - | 23 | 72 | <0.01 |
| Smoking | - | - | - | 8 | 10 | N.S |
| FH of CVD | - | - | - | 43 | 44 | N.S |
| DBP (mmHg) | - | - | - | 10 | 7 | N.S |
| Magnussen 2009 | Age (year) | - | - | - | 40.1 | 39.9 | N/A |
| Current antihypertensive | - | - | - | 9.6 | 2.2 | N/A |
| Smoking | - | - | - | 26.4 | 37.3 | N/A |
| Education 14+ years (%) | - | - | - | 10.1 | 9.4 | N/A |
| Hashemi 2012 | Not available | - | - | - | - | - | - |
| Savitz 2014 | Not available | - | - | - | - | - | - |
| Tam 2015 | Not available | - | - | - | - | - | - |

BMI=body mass index, CVD=cardiovascular disease, DBP=diastolic blood pressure, DM=diabetes mellitus, E=PE in early pregnancy, FH=family history, HDL=high density lipoprotein, HTN=hypertension, HOMA-IR=homeostatic model assessment-insulin resistance, L=PE in late pregnancy, LDL=low density lipoprotein, MAP=mean arterial pressure, MI=myocardial infarction, N.S=non-significant, PE=pre-eclampsia, SBP=systolic blood pressure.

**Appendix 1.** Search terms.

Synonyms of pre-eclampsia (‘preeclampsia’ or ‘pre-eclampsia’ or ‘EPH’ or ‘pregnancy toxemia’ or ‘edema-proteinuria-hypertension gestos’) AND ‘hypertension’ or ‘diabetes’ or ‘ischaemic heart disease’ or ‘ischemic heart disease’ or ‘coronary artery disease’ or ‘coronary heart disease’ or ‘myocardial infarction’ or ‘acute coronary syndrome’ or ‘heart failure’ or ‘cardiac failure’ or ‘left ventricular systolic dysfunction’ or ‘stroke’ or ‘cerebrovascular disease’ or ‘cerebrovascular accident’ or ‘pulmonary embolus’ or ‘venous thromboembolism’ or ‘deep vein thrombosis’ or ‘cardiomyopathy’ or ‘renal impairment’ or ‘kidney disease’ or ‘peripheral vascular disease’.

To ensure a comprehensive search strategy, we also searched for synonyms of hypertensive disorders of pregnancy (‘pregnancy induced hypertension’ or ‘pregnancy-induced hypertension’ or ‘hypertensive disorder$ pregnancy’ or ‘hypertensive disorder$ of pregnancy’ or ‘hypertensive disorder$ in pregnancy’ or ‘hypertensive disorder$ complicating pregnancy’ or ‘hypertension in pregnancy’ or ‘hypertension pregnant women’ or ‘hypertension pregnancy’ or ‘hypertension pregnancy-induced’ or ‘pregnancy hypertension’ or ‘hypertensive pregnancy disorder$’ or ‘pregnancy-related hypertensive disorder$’) AND diabetes.