

Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis

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ABSTRACT

Objective To quantify the risk of future cardiovascular diseases, cancer, and mortality after pre-eclampsia.

Design Systematic review and meta-analysis.

Data sources Embase and Medline without language restrictions, including papers published between 1960 and December 2006, and hand searching of reference lists of relevant articles and reviews for additional reports.

Review methods Prospective and retrospective cohort studies were included, providing a dataset of 3 488 160 women with 198 252 affected by pre-eclampsia (exposure group) and 29 495 episodes of cardiovascular disease and cancer (study outcomes).

Results After pre-eclampsia women have an increased risk of vascular disease. The relative risks (95% confidence intervals) for hypertension were 3.70 (2.70 to 5.05) after 14.1 years weighted mean follow-up, for ischaemic heart disease 2.16 (1.86 to 2.52) after 11.7 years, for stroke 1.81 (1.45 to 2.27) after 10.4 years, and for venous thromboembolism 1.79 (1.37 to 2.33) after 4.7 years. No increase in risk of any cancer was found (0.96, 0.73 to 1.27), including breast cancer (1.04, 0.78 to 1.39) 17 years after pre-eclampsia. Overall mortality after pre-eclampsia was increased: 1.49 (1.05 to 2.14) after 14.5 years.

Conclusions A history of pre-eclampsia should be considered when evaluating risk of cardiovascular disease in women. This association might reflect a common cause for pre-eclampsia and cardiovascular disease, or an effect of pre-eclampsia on disease development, or both. No association was found between pre-eclampsia and future cancer.

INTRODUCTION

Changes during healthy pregnancy include insulin resistance, hyperlipidaemia, hypercoagulability, inflammation, and a hyperdynamic circulation. These are exaggerated in women with pre-eclampsia and some are also features of the "metabolic syndrome," a risk factor for cardiovascular disease.¹ It is possible that pre-eclampsia increases risk of later cardiovascular disease² either because of a shared cause or because subclinical vascular damage occurs during pre-eclampsia.

We carried out a systematic review and meta-analysis of studies that estimated the risk of arterial and venous diseases after pre-eclampsia. We also evaluated the risk of future cancer after pre-eclampsia,

in particular breast cancer.³ Finally we investigated mortality from any cause after pre-eclampsia.

METHODS

We searched Medline and Embase up to December 2006 for prospective and retrospective cohort studies assessing women of any parity or age or with any severity of pre-eclampsia. The study had to identify pre-eclampsia as the risk factor under investigation and have incident disease as the outcome.

Pre-eclampsia was normally defined as the onset of blood pressure >140/90 mm Hg with proteinuria >0.3 g/24 h after 20 weeks' gestation.⁴ We included a separate analysis of studies that had followed up women with isolated pregnancy induced hypertension. The comparator group were women who completed pregnancies without pre-eclampsia. Outcomes were hypertension, fatal or non-fatal ischaemic heart disease, stroke, venous thromboembolism, breast cancer, any cancer, and total mortality. Ischaemic heart disease events included myocardial infarction, angina, coronary artery bypass grafting, severe coronary artery ischaemia, and heart failure. Stroke included both haemorrhagic and ischaemic cerebrovascular events. Venous thromboembolism included all deep vein thromboses and pulmonary emboli. Breast cancer was defined as a diagnosis of the cancer or resulting death after the index pregnancy.

We utilised the inverse variance weighted method to obtain summary relative risks and 95% confidence intervals, using random effects models for all analyses. The extent of adjustment for confounding was recorded. We evaluated small study bias using funnel plots and an Egger test. For each outcome we calculated a weighted mean follow-up in years. We used Revman 4.2.7 and Stata 9.0.

Heterogeneity was assessed by Q test and I² tests. We explored sources of heterogeneity by evaluating the robustness of the estimate of the effect according to prespecified subgroups by parity, severity of pre-eclampsia, and severity of disease outcome. We extracted relevant study characteristics for definition of exposure, outcome, sample size (number of incident cases), and degree of confounding, and we used these in a sensitivity analysis.

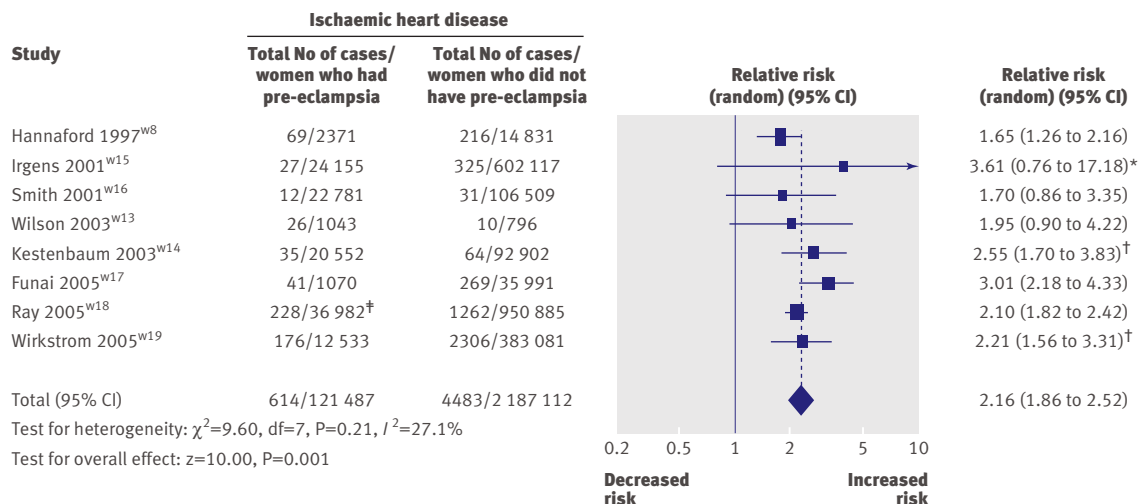


Fig 1 | Pre-eclampsia and risk of fatal and non-fatal ischaemic heart disease events in later life. *Early and late pre-eclampsia combined (see table 2 on bmj.com). †Mild and severe pre-eclampsia combined (see table 2 on bmj.com). ‡All maternal placental syndromes

RESULTS

Twenty five studies met the inclusion criteria involving 29 495 incident cases of cardiovascular diseases and cancers among 3 488 160 women (see bmj.com), of whom 198 252 had pre-eclampsia.

Pre-eclampsia and risk of future hypertension

In 13 studies (21 030 women) evaluating risk of hypertension, 3658 women had pre-eclampsia and 1885 women developed hypertension (see bmj.com).^{w1-w13} The mean weighted follow-up was 14.1 years.

The relative risk of later hypertension after pre-eclampsia was 3.70 (95% confidence interval 2.70 to 5.05) compared with women who did not develop pre-eclampsia. Significant heterogeneity was observed ($P=0.001$, $I^2=62.6\%$; see bmj.com), with evidence that small studies reported larger effect sizes (Egger test, $P=0.014$).

Analysis according to parity indicated a higher relative risk of hypertension after pre-eclampsia in any pregnancy (four studies^{w2 w5 w10 w11}; 5.96, 3.42 to 10.38) compared with pre-eclampsia in the first pregnancy only (nine studies^{w1 w3 w4 w6-w9 w12 w13}; 3.23, 2.32 to 4.52; $\chi^2=8.48$, $P=0.004$).

Pre-eclampsia and risk of ischaemic heart disease later life

Eight studies (2 346 997 women) contributed to the analysis of fatal and non-fatal ischaemic heart disease (see bmj.com),^{w8 w13 w19} with 121 487 women who developed pre-eclampsia and 5097 ischaemic heart disease events. The weighted mean follow-up was 11.7 years. The relative risk of fatal or non-fatal ischaemic heart disease in women with previous pre-eclampsia was over twice that of women who did not develop pre-eclampsia (2.16, 1.86 to 2.52). No substantial heterogeneity was observed ($P=0.21$, $I^2=27.1\%$; fig 1). No evidence of small study bias was found (Egger test, $P=0.59$), and no clear asymmetry was observed in the funnel plot.

Six studies assessed primiparous women with pre-eclampsia^{w13-w16 w18 w19} and two assessed women with pre-eclampsia in any pregnancy.^{w8 w17} The risks of ischaemic heart disease were similar in both groups (primiparous women: 1.89, 1.40 to 2.55; any pregnancy: 2.23, 1.21 to 4.09).

The risk of future fatal ischaemic heart disease events was increased in women after pre-eclampsia. In four studies^{w13 w15-w17} a summary relative risk of 2.60 (1.94 to 3.49) was identified for a fatal event. Four other studies included fatal and non-fatal ischaemic heart disease as their outcome^{w8 w14 w18 w19}: relative risk (2.17, 1.92 to 2.45; see bmj.com).

In two studies^{w15 w16} pre-eclampsia before 37 weeks' gestation was associated with nearly an eightfold increased risk of ischaemic heart disease (7.71, 4.40 to 13.52) compared with women with normal blood pressure completing pregnancies after 37 weeks (see bmj.com).

The severity of pre-eclampsia also increased the risk of later ischaemic heart disease but not to the same extent as the gestation of onset. Two studies^{w14 w19} showed that women with severe pre-eclampsia (blood pressure >160/110 mm Hg plus proteinuria >0.3 g/24 h^{w14} or diastolic blood pressure >110 mm Hg plus proteinuria >5 g/24 h^{w20}) had a greater risk of later ischaemic heart disease (2.86, 2.25 to 3.65) compared with women with mild pre-eclampsia (1.92, 1.65 to 2.24; see bmj.com).

Pre-eclampsia and risk of stroke in later life

Four studies (1 671 578 women) were included involving 64 551 women with pre-eclampsia and 907 incident strokes (see bmj.com).^{w8 w13 w15 w18} The mean weighted follow-up was 10.4 years. The overall risk of fatal and non-fatal stroke after pre-eclampsia was 1.81 (1.45 to 2.27) compared with women who did not develop pre-eclampsia. No heterogeneity was observed ($P=0.51$; $I^2=0\%$; see bmj.com) and no evidence of small study bias was found (Egger test, $P=0.82$).

Two studies reported on the risk of fatal stroke^{w13 w15} and three examined non-fatal events.^{w8 w13 w18} The risk of fatal stroke was greater than the risk of a non-fatal event after pre-eclampsia (2.98, 1.11 to 7.96 and 1.76, 1.40 to 2.22).

A diagnosis of pre-eclampsia before 37 weeks' gestation^{w15} was associated with a higher risk of stroke in later life (5.08, 2.09 to 12.35) compared with a diagnosis of pre-eclampsia after 37 weeks' gestation (0.98, 0.50 to 1.92); P for heterogeneity 0.004; I²=88.1%).^{w15}

Pre-eclampsia and risk of venous thromboembolism in later life

Three studies (427 693 women) involving 35 772 women with pre-eclampsia and 470 incident cases of venous thromboembolism were analysed (see bmj.com).^{w8 w14 w20} The weighted mean follow-up was 4.7 years. The risk of venous thromboembolism in women who developed pre-eclampsia was 1.79 (1.37 to 2.33) compared with women who did not develop pre-eclampsia. No heterogeneity was observed (P=0.65; I²=0%; see bmj.com).

In one study severe pre-eclampsia was associated with a higher risk of venous thromboembolism in later life (2.3, 1.3 to 4.2) compared with mild pre-eclampsia (1.4, 0.9 to 2.2).^{w14}

Pre-eclampsia and risk of future cancer

Breast cancer

Four studies (776 445 women) including 46 593 with pre-eclampsia and 7468 incident events of breast cancer were analysed (see bmj.com).^{w21-w24} The average mean weighted follow-up was 17 years. The relative risk of women who had pre-eclampsia developing breast cancer in later life was 1.04 (0.78 to 1.39). Small study bias

was not present (Egger test, P=0.37) although important heterogeneity was observed (P=0.006; I²=75.7%; fig 2). This heterogeneity was not explained by parity. No difference was found in the estimate of the effect between three studies that included women with pre-eclampsia in any pregnancy^{w21 w22 w24} (1.04, 0.78 to 1.39) and one study that assessed only primiparous women (0.81, 0.72 to 0.92).^{w23}

Any cancer

Three studies (729 025 women) were included involving 41 084 women with pre-eclampsia and 6131 incident cancers^{w15 w17 w25} (see bmj.com). The average mean weighted follow-up for each woman was 13.9 years. The relative risk of developing any cancer after pre-eclampsia was 0.96 (0.73 to 1.27). No evidence was found of heterogeneity (P=0.15; I²=43.2%; fig 2) or of small study bias (Egger test, P=0.97).

Pre-eclampsia and all cause mortality in later life

Four studies (794 462 women) included 49 049 with pre-eclampsia; and 7537 women later died^{w13 w15-w17} (see bmj.com). The average mean weighted follow-up was 14.5 years. Women who developed pre-eclampsia had an increased risk of death from any cause compared with women who did not develop pre-eclampsia (1.49, 1.05 to 2.14). Heterogeneity was substantial (P<0.00001; I²=93.9%; see bmj.com) and this was most noticeable between studies of early and late pre-eclampsia (P<0.00001; I²=96.5%). Women developing pre-eclampsia before 37 weeks' gestation had a relative risk of 2.71 (1.99 to 3.68) of death from any cause in later life compared with women who had normal blood pressure completing pregnancies.^{w15} No evidence of small study bias was found (Egger test, P=0.84).

DISCUSSION

A history of pre-eclampsia increases the risk of future hypertension, ischaemic heart disease, stroke, venous thromboembolism, and death. The major contribution to all cause mortality seems to be cardiovascular disease.

It is possible that much of the excess risk of future ischaemic heart disease and stroke is explained by the link between pre-eclampsia and blood pressure. Most studies only adjusted for age, but three adjusted for diabetes mellitus, features of the metabolic syndrome, smoking, and socioeconomic status.^{w9 w17 w18} In one of these studies (over a million women) the association between pre-eclampsia and cardiovascular disease was independent of prepregnancy hypertension, diabetes mellitus, obesity, dyslipidaemia, the metabolic syndrome, and smoking.^{w18} We found a similar twofold increased risk of cardiovascular disease in those studies with incomplete adjustment for established cardiovascular risk factors.

Women who had pre-eclampsia early (<37 weeks) in their first pregnancy were more likely to have recurrent pre-eclampsia than those who had pre-eclampsia later in their first pregnancy. Recurrent pre-eclampsia compared with a single episode has been associated with a sevenfold increased risk of later hypertension.^{w3} We also

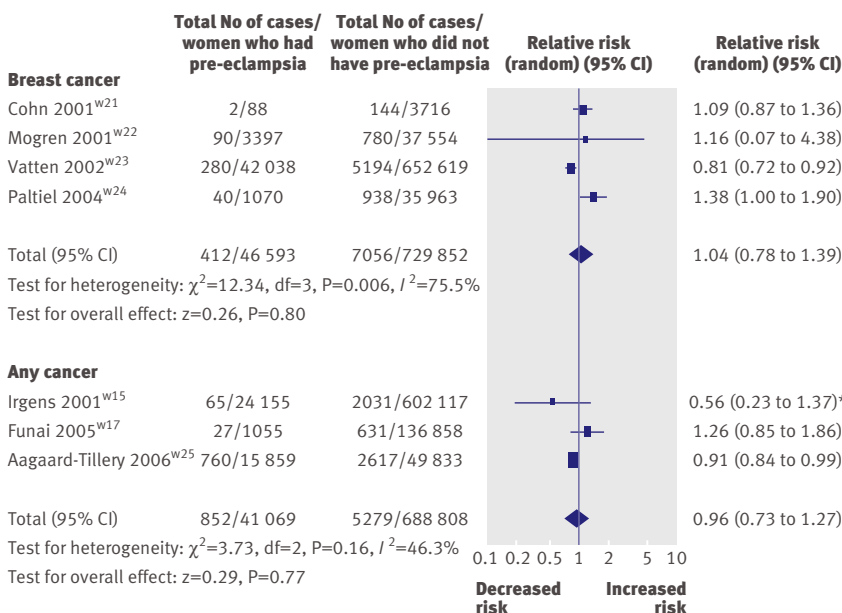


Fig 2 | Pre-eclampsia and risk of breast cancer or any cancer in later life. *Early and late pre-eclampsia combined

WHAT IS ALREADY KNOWN ON THIS TOPIC

A positive association has been found between pre-eclampsia and future cardiovascular disease but individual studies have had too few incident events to estimate the risks with precision

It is uncertain whether the association is specific to cardiovascular diseases or extends to other common life threatening disorders such as cancer

WHAT THIS STUDY ADDS

After pre-eclampsia women have an increased risk of hypertension, fatal and non-fatal ischaemic heart disease, stroke, and venous thromboembolism in later life

Early onset pre-eclampsia (<37 weeks' gestation) is associated with an even greater risk of future cardiovascular disease

No association was found between pre-eclampsia and future breast cancer

found that pre-eclampsia in any pregnancy compared with pre-eclampsia in only the first pregnancy was associated with a greater relative risk of future hypertension.

We also observed in the sensitivity analysis that women who had early pre-eclampsia had the greatest risk of future cardiovascular disease and this was higher than those who had "severe" pre-eclampsia. This observation was supported by tests of heterogeneity.

Most women in the studies in our review will not have reached the menopause by the time of follow-up, so their absolute risk of ischaemic heart disease is likely to have been low. Two reports included in our review followed up women for more than 20 years after pre-eclampsia and the twofold risk of later cardiovascular disease seems to persist long term.^{w13 w17}

Most populations included in the systematic review were of European origin. It is possible that other ethnic groups will have different risk ratios for future cardiovascular disease.

The null association with cancer, a common cause of morbidity and mortality in later life, suggests the associations are specific to cardiovascular disease. This may indicate a common cause for pre-eclampsia and cardiovascular disease or a deleterious effect of pre-eclampsia on the maternal vascular system, or both.

It is possible that transient but severe endothelial dysfunction, observed in pre-eclampsia,⁵ potentiates a cascade of events that progresses to atherosclerosis. Endothelial dysfunction has been observed as early as 23 weeks' gestation in women who develop pre-eclampsia later, during pre-eclampsia itself, and at least three months after pre-eclampsia has resolved.⁵⁻⁷

It is possible therefore that pre-eclampsia is the initial point of expression of an inherent adverse phenotype associated with the early development of cardiovascular disease.

It is unlikely that our observations are the result of chance because of the large number of women included (>3.4 million) and the large number of incident cases. Furthermore, there was a strong consistency of the association between pre-eclampsia and future cardiovascular disease in different studies for most end points. The only outcome for which there was evidence of small study bias was incident hypertension (see [bmj.com](#)).⁸ Clear concordance was, however, found between the effect

estimates of the largest studies included in the meta-analyses and the overall relative risks that we produced for each outcome.

The application of a quantitative score of study quality as part of study selection in meta-analysis is not a validated process and can introduce bias. We therefore evaluated in a sensitivity analysis those study characteristics that may introduce bias (see [fig 4 on bmj.com](#)). This approach indicated that the findings were robust.

Some women in older studies with pregnancy induced hypertension may have been misclassified as having pre-eclampsia, but when analyses were restricted to women with a clear phenotype such as severe pre-eclampsia, similar results were obtained. Furthermore, we showed that women who had pregnancy induced hypertension have a similar, but lower, risk of future hypertension and cardiovascular disease as those who had rigorously defined pre-eclampsia (see [bmj.com](#)).

Conclusions

Women who have had pre-eclampsia have an increased risk of cardiovascular disease, including an almost fourfold increased risk of hypertension and an approximately twofold increased risk of fatal and non-fatal ischaemic heart disease, stroke, and venous thromboembolism in later life. This may explain the small increase in risk of death after pre-eclampsia. The lack of association between pre-eclampsia and future cancer, in particular breast cancer, suggests a specific relation between pre-eclampsia and cardiovascular disease.

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