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

Leanne Bellamy, medical student,[1] Juan-Pablo Casas, clinical lecturer,[2] Aroon D Hingorani, reader,[3] David J Williams, consultant obstetric physician[4]

[1]Imperial College School of Medicine, London
[2]Department of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine
[3]British Heart Foundation Laboratories, Department of Medicine, University College London
[4]Institute for Women's Health, Elizabeth Garrett Anderson Obstetric Hospital, University College London, London WC1E 6DH

Correspondence to: D J Williams
d.williams@uclh.nhs.uk

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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

Pre-eclampsia is a syndrome of pregnancy defined by the onset of hypertension and proteinuria and characterised by widespread dysfunction of the endothelium in the mother.[1 2] In the developed world pre-eclampsia affects 3-5% of first pregnancies.[3] Worldwide the hypertensive disorders of pregnancy are more common and are responsible for 12% of maternal mortality during pregnancy and the puerperium.[4]

Changes during healthy pregnancy include insulin resistance,[5] hyperlipidaemia,[6] hypercoagulability,[7] inflammation,[8] and a hyperdynamic circulation[9]. These are exaggerated in women with pre-eclampsia and some are also features of the "metabolic syndrome" a "risk factor" for cardiovascular disease.[10] It is possible that pre-eclampsia increases risk of later cardiovascular disease,[11] either because of a shared cause or because subclinical vascular damage occurs during pre-eclampsia.

If a history of pre-eclampsia exerts an independent risk for future cardiovascular disease it may increase the risk of cardiovascular disease in mid-life in affected women, which would render them eligible for preventive therapies at an earlier age than usual. To investigate the association between pre-eclampsia and atherosclerosis in later life we carried out a systematic review and meta-analysis of studies that had 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, one of the commonest causes of death in middle aged women.[13 14] Finally we investigated mortality from any cause after a pregnancy affected by pre-eclampsia.

METHODS

We searched Medline and Embase with no language restrictions up to December 2006. Additional eligible studies were sought by a hand search of reference lists from primary articles and relevant reviews. (See bmj.com for search terms and combinations).

We included prospective and retrospective cohort studies assessing women of any parity or age or with any severity of pre-eclampsia. To minimise selection or recall bias we excluded case-control studies. We defined a cohort study (including nested case-control and case cohorts) as one that identified pre-eclampsia as the risk factor under investigation and aimed to identify incident disease as the outcome.

Pre-eclampsia was normally defined as the onset of a blood pressure level exceeding 140/90 mm Hg with proteinuria greater than 0.3 g/24 h after 20 weeks' gestation.[2] Studies included before 2001 were less exact about the diagnosis of pre-eclampsia, so it is possible that a proportion of cases of pregnancy induced hypertension were misclassified as pre-eclampsia. For this reason we included a separate analysis of studies that had followed up women with isolated pregnancy induced hypertension, defined as the onset of a blood pressure exceeding

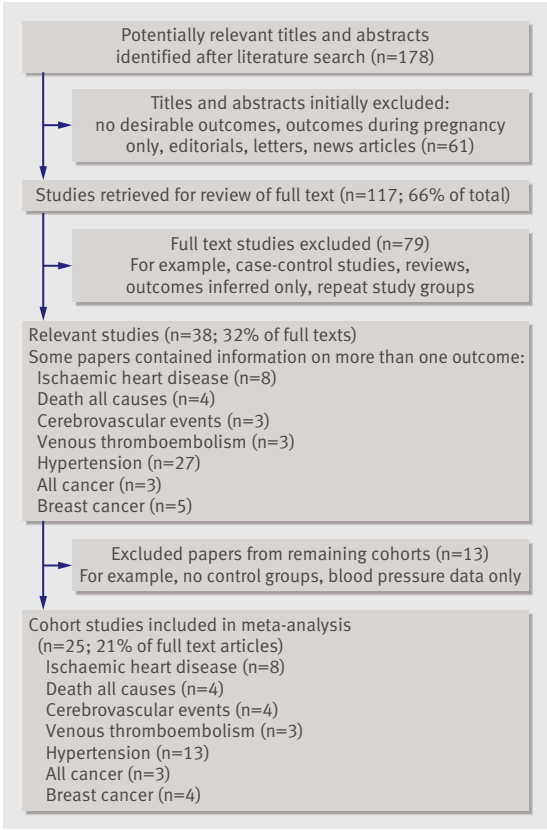

Fig 1 | **Study selection process**

140/90 mm Hg in the absence of proteinuria after 20 weeks' gestation. Severe pre-eclampsia was defined as a blood pressure exceeding 160/110 mm Hg or proteinuria greater than 5 g/24 h, or both. The comparator group were women who completed pregnancies without developing pre-eclampsia. Outcomes evaluated 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. All outcomes were classified according to the World Health Organization's international classification of disease criteria. As pre-eclampsia resolves within three months of delivery,[15 16] we limited analyses to studies that evaluated outcomes developing after this interval. We excluded studies with historical controls.[17]

Two assessors (LB and JPC) evaluated each included full text article independently and extracted and tabulated all relevant data. Inconsistencies were checked and settled by consensus with all four authors. For additional reports relating to the original cohort, we included the report with the most information relevant to the study question.

We contacted seven authors from six of the included studies [w8 w13 w15 w16 w20 w22] and received additional unpublished data on numbers of exposed women, incident cases of cardiovascular disease and cancer, and relative risks for studied outcomes.

All procedures and reporting conformed to the meta-analysis of observational studies in epidemiology guidelines.[18] We excluded 13 unsuitable studies—one with no incident cases in study groups of women who had had pre-eclampsia compared with those who had not had pre-eclampsia, four that reported blood pressure only for both study groups together at follow-up, and eight without control populations.

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 carried out at the level of individual studies was recorded and tabulated. We evaluated small study bias for each outcome by visualisation of funnel plots and an Egger test (by regressing the log relative risk against its standard error; see bmj.com for funnel plot analyses). For each outcome we calculated a weighted mean follow-up in years. We used Revman 4.2.7 and Stata 9.0 for statistical analyses.

Heterogeneity was assessed by Q test and I^2 tests. We explored sources of heterogeneity between study groups 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. Instead of generating quality scores for included studies (a controversial approach in synthesis research), 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.

RESULTS

Overall 117 full text articles were identified. Thirty eight studies met the inclusion criteria, of which 25 were included. These studies included 29 495 incident cases of cardiovascular diseases and cancers among 3 488 160 women, of whom 198 252 had pre-eclampsia and over 3 million did not (comparator group; fig 1).

Pre-eclampsia and risk of future hypertension

In 13 studies (21 030 women) fulfilling the criteria for risk of future hypertension, 1885 of 3658 women who had pre-eclampsia developed chronic hypertension in later life (table 1).[w1-w13] The mean weighted follow-up was 14.1 years.

The relative risk of a later diagnosis of hypertension in women 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%; fig 2), with evidence that small studies reported larger effect sizes

(Egger test, P=0.014). In analyses stratified according to the total number of cases, a smaller risk for hypertension (2.37, 2.11 to 2.66) was obtained after pooling the two large studies, each with more than 200 cases, compared with the risk from pooling 11 small studies, each with fewer than 200 cases (4.43, 3.24 to 6.05).

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; χ^2=8.48, P=0.004).

Pregnancy induced hypertension and risk of future hypertension

Early studies are likely to have misclassified some women with pregnancy induced hypertension as having had pre-eclampsia. Two studies, totalling 2106 women, investigated the association between a history of pregnancy induced hypertension and future hypertension; 454 women had had pregnancy induced hypertension and 300 incident cases of hypertension occurred within 10.8 years. The relative risk of incident hypertension for women who had pregnancy induced hypertension compared with women who did not was

Table 1 | **Pre-eclampsia and risk of hypertension in later life**

					Definition of exposure						
Study, country	Study design	Exposure	Race	Parity	Minimum SBP, minimum DBP (mm Hg)	Minimum proteinuria g/24 h	No with pre-eclampsia/No of women	Mean follow-up (years)	No with hypertension	Relative risk (95% CI)	Extent of adjustment*
Adams 1961,[w1] UK	RC	Pre-eclampsia	White	P	—, 90	0.25	53/334†	17.6	61‡	5.91 (3.89 to 8.98)	
Epstein 1964,[w2] USA	RC	Pre-eclampsia	White	Any	§, §	‡	48/162†	15	44	5.34 (2.50 to 11.44)	
Sibai 1986,[w3] USA	PC	Pre-eclampsia and eclampsia	Mixed	P	160, 110	1	406/815	7.3	83	2.63 (1.66 to 4.17)	
Carleton 1988,[w4] USA	RC	Pre-eclampsia	Mixed	P	—, 85	1	23/46	10.4	5	1.50 (0.28 to 8.16)	Body mass index
Nisell 1995,[w5] Sweden	RC	Pre-eclampsia	White	Any	140, 90	0.3	45/89	7	10	8.80 (1.16 to 66.59)	
North 1996,[w6] New Zealand	RC	Pre-eclampsia	Non-white group	P	140, 90	0.3	50/100	5	21	20.00 (2.79 to 143.38)	
Laivuori 1996,[w7] Finland	RC	Pre-eclampsia	White	P	160, 110	0.3	22/44	17	2¶	5.00 (0.25 to 98.52)	
Hannaford 1997,[w8] UK	PC	Pre-eclampsia	Mixed	Any	140, 90	0.3	2371/17 202	12.5**	1299††	2.35 (2.08 to 2.65)	Smoking, socioeconomic status
Marin 2000,[w9] Spain	RC and PC	Pre-eclampsia	White	P	140, 90	0.3	80/166	14.2	42††	3.70 (1.72 to 7.97)	Body mass index, socioeconomic status, hypercholesterolaemia, type 2 diabetes mellitus
Shammas 2000,[w10] Jordan	RC	Pre-eclampsia	Mixed	Any	Diagnosis of pre-eclampsia in medical records	Diagnosis of pre-eclampsia in medical records	47/93	10	26	7.50 (2.42 to 23.28)	
Hubel 2000,[w11] Iceland	RC	Eclampsia	White	Any	140, 90	‡	30/60	32.65	12‡‡	5.00 (1.19 to 20.92)	
Sattar 2003,[w12] Scotland	RC	Pre-eclampsia	White	P	140, 90	0.3	40/80	19	9‡‡	3.50 (0.77 to 15.83)	Body mass index, smoking
Wilson 2003,[w13] Scotland	RC	Pre-eclampsia and eclampsia	White	P	—, 90	0.3	443/1839	32	271§§	2.62 (1.77 to 3.86)	Socioeconomic status
Total							3658/21 030¶¶	14.1	1885		

SBP=systolic blood pressure; DBP=diastolic blood pressure; RC=retrospective cohort; P=primiparous; PC=prospective cohort. All papers adjusted/matched for maternal age, parity, year of birth, and hospital of delivery.
*Women with pregnancy induced hypertension who had been classified as mild pre-eclampsia were excluded.
†List of variables used in individual studies to adjust for effect of pre-eclampsia on later risk of chronic disease.
‡Diagnosis "eclampsia," proteinuria not recorded.
§New onset hypertension, proteinuria, and oedema in third trimester.
¶Number of cases of hypertension in control group.
**Calculated from total number of woman years.
††Codes 400-404 from international classification of diseases, ninth revision.
‡‡Hypertension defined by hypertensive prescribed.
§§Codes 401-404 from international classification of diseases, ninth revision.
¶¶21 030 women were reviewed, but 19 744 were included in meta-analysis. 296 women with pregnancy induced hypertension were excluded.

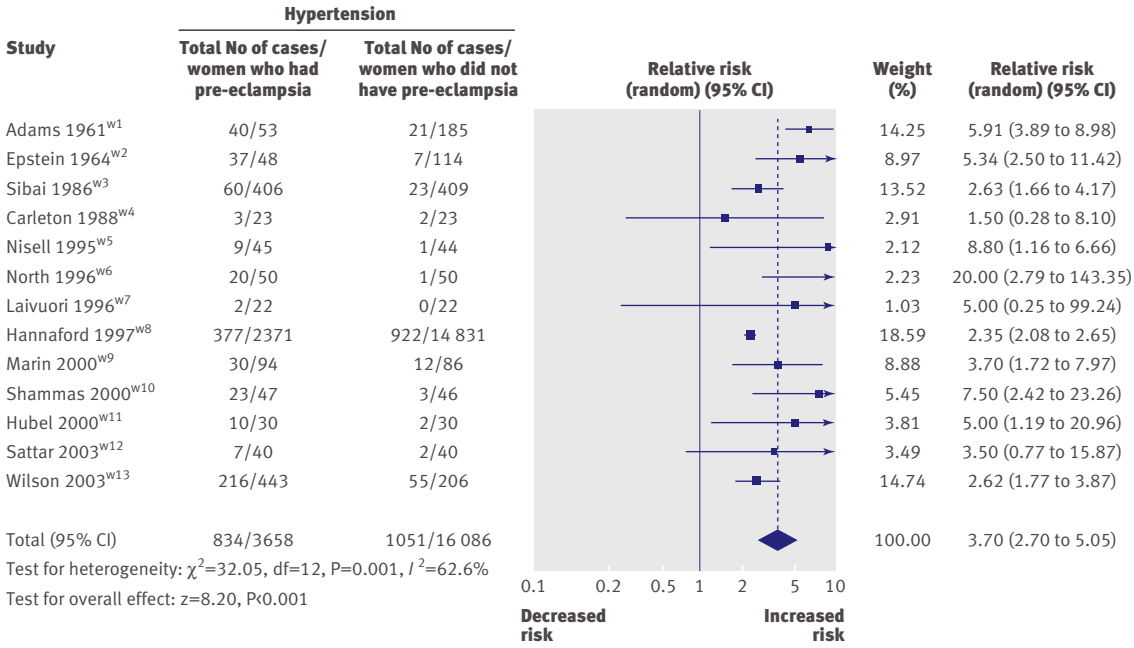

Fig 2 | Pre-eclampsia and risk of hypertension in later life

3.39 (0.82 to 13.92; P for heterogeneity=0.0006, I^2=91.4%; see bmj.com).[w9 w13] The increase in risk for future cardiovascular disease was 1.66 (0.62 to 4.41; P for heterogeneity=0.10, I^2=63.8%; see bmj.com).[w13 w14]

Pre-eclampsia and risk of ischaemic heart disease in later life

Eight studies (2 346 997 women) contributed to the analysis of fatal and non-fatal ischaemic heart disease (table 2),[w8 w13 w19] with 121 487 women having had 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 had not developed pre-eclampsia (2.16, 1.86 to 2.52). No substantial heterogeneity was observed (P=0.21, I^2=27.1%; figs 3 and 4). The Egger regression test showed no evidence of small study bias (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: for primiparous women with pre-eclampsia the risk was 1.89 (1.40 to 2.55) and for women with pre-

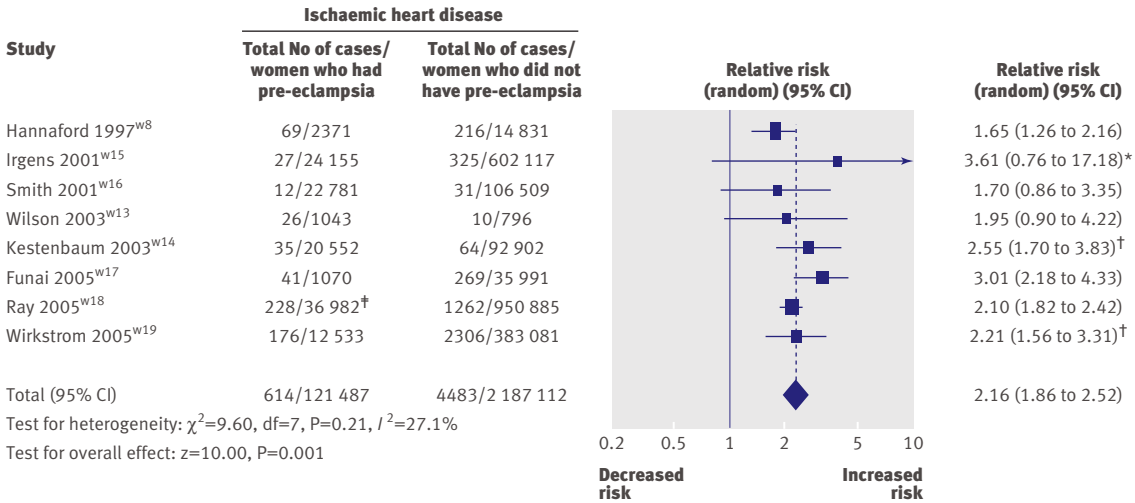

Fig 3 | Pre-eclampsia and risk of fatal and non-fatal ischaemic heart disease events in later life. *Early and late pre-eclampsia combined (see table 2). †Mild and severe pre-eclampsia combined (see table 2). ‡All maternal placental syndromes

eclampsia in any pregnancy the risk was 2.23 (1.21 to 4.09; fig 4).

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 after pre-eclampsia[w8 w14 w18 w19] (relative risk 2.17, 1.92 to 2.45; fig 4).

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' gestation (fig 4).

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

Table 2 | **Pre-eclampsia and risk of ischaemic heart disease in later life**

Study, country	Study design	Condition	Race	Parity	Definition of exposure		No with pre-eclampsia/ No of women	Mean follow-up (years)	Primary outcome	No of cases	Relative risk (95% CI)	Degree of adjustment*
					Minimum SBP, minimum DBP (mm Hg)	Minimum proteinuria g/24 h						
Hannaford 1997 UK[w8]	PC	Pre-eclampsia	Mixed	Any	140, 90	0.3	2371/17 202	12.5†	Total IHD	310	1.65 (1.26 to 2.16)	Smoking, socioeconomic status
Irgens 2001 Norway[w1]	RC	Pre-eclampsia 16-36 weeks; pre-eclampsia ≥ 37 weeks	White	P	—, 85	—	2649; 21 506/ 626 272	13	IHD death‡	50; 302	8.12 (4.31 to 15.33); 1.65 (1.01 to 2.7)	
Smith 2001 UK[w17]	RC	Pre-eclampsia	White	P	§, §	§	22 781/129 290	16.9	IHD death¶	43	1.7 (0.9 to 3.35)	Socioeconomic status
Wilson 2003 UK[w14]	RC	Pre-eclampsia and eclampsia	White	P	—, 90	0.3	1043/1839	32	IHD death**	36	1.95 (0.90 to 4.22)	Socioeconomic status
Kestenbaum 2003 USA[w15]	RC	Mild pre-eclampsia; severe pre-eclampsia and eclampsia	Mixed	P	140, 90; 160, 110	0.3; 0.3	15 508; 5044/ 113 454	7.8	IHD event††	88; 75‡‡	2.2 (1.3 to 3.6); 3.3 (1.7 to 6.5)	
Funai 2005 Israel[w18]	RC	Pre-eclampsia	Mixed	Any	140, 90	§§	1070/37 061	30	IHD death¶	310	3.07 (2.18 to 4.33)	Socioeconomic status, type 2 diabetes mellitus, gestational diabetes
Ray 2005 Canada[w19]	RC	Pre-eclampsia	Mixed	P	140, 90	0.3	36 982/1 026 265	8.7	IHD event¶¶	1490	2.1 (1.82 to 2.42)	Smoking, socioeconomic status, gestational diabetes, obesity hypertension, dyslipidaemia, type 2 diabetes mellitus, renal disease
Wikström 2005 Sweden[w20]	RC	Mild pre-eclampsia; severe pre-eclampsia and eclampsia	White	P	140, 90; —, 110	0.3; 0.5	9718; 2815/ 395 614	15	Total IHD¶	2429; 2359	1.9 (1.6 to 2.2); 2.8 (2.2 to 3.7)	Socioeconomic status
Total							121 487/2 346 997***	11.7	IHD cases	5097		

SBP=systolic blood pressure, DBP= diastolic blood pressure; PC=prospective cohort; IHD=ischaemic heart disease; RC=retrospective cohort; P=primiparous. All papers adjusted for maternal age, year of birth, and hospital of delivery.
*List of variables used in individual studies to adjust for effect of pre-eclampsia on later risk of chronic disease.
§Hypertension, proteinuria or albuminuria, or both from Scottish morbidity records.
†Calculated from total number of woman years.
‡Codes 410-429 from international classification of diseases, eighth and ninth revisions.
¶Codes 410-414 from international classification of diseases, ninth revision, and codes 20-25 from 10th revision.
††Codes 410, 36 (coronary artery bypass graft), 430, 431, 434, 436 from international classification of diseases, ninth revision (stroke included as cardiovascular disease).
§§Proteinuria (and oedema) must be present, no minimum value specified.
**Codes 410-4.428 from international classification of diseases, ninth revision and codes I20-25 and I50 from international classification of diseases, 10th revision.
¶¶Codes 410, 411, 413, 414, and 48 from international classification of diseases, ninth revision and codes I20, I21, I24, I25.0, and I25.1 and respective ICD-10 revisions.
***2 346 997 women were reviewed, but 2 308 599 were included in meta-analysis. 38 398 non-pre-eclamptic women with maternal placental syndrome were excluded (see Ray 2005[w19])
‡‡Same control group was used for mild and severe pre-eclampsia (99 cases; see fig 3).

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; fig 4).

Pre-eclampsia and risk of stroke in later life

Four studies (1 671 578 women) were included involving 64 551 women who had pre-eclampsia and 907 incident strokes (table 3).[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%; fig 5) 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; I^2=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 (table 4).[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; I^2=0%; fig 5).

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 (table 5).[w21-w24] The average weighted mean follow-up for each woman 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; I^2=75.7%; fig 6). This heterogeneity was not explained by parity. No difference was found in the estimate of the

Table 3 | Pre-eclampsia and risk of fatal and non-fatal stroke in later life

Study, country	Study design	Exposures	Race	Parity	Definition of exposure: Minimum SBP, minimum DBP (mm Hg)	Definition of exposure: Minimum proteinuria g/24 h	No with pre-eclampsia/ No of women	Mean follow-up (years)	Primary outcome	No of cases	Relative risk (95% CI)	Degree of adjustment*
Hannaford 1997,[w8] UK	PC	Pre-eclampsia	Mixed	Any	140, 90	0.3	2371/17 202	12.5†	Non-fatal haemorrhagic or ischaemic stroke‡	118	1.39 (0.89 to 2.17)	Smoking, socioeconomic status
Irgens 2001,[w16] Norway	RC	Pre-eclampsia 16-36 weeks; pre-eclampsia ≥37 weeks	White	P	—, 85	—	2649; 21506/626 272	13	Fatal stroke§	29; 277	5.08 (2.09 to 12.35); 0.98 (0.5 to 1.91)	
Wilson 2003,[w14] UK	RC	Pre-eclampsia and eclampsia	White	P	—, 90	0.3	1043/1839	32	Non-fatal haemorrhagic or ischaemic stroke§; fatal haemorrhagic or ischaemic stroke§	47; 21	2.1 (1.02 to 4.32); 3.59 (1.04 to 1.4)	Socioeconomic status
Ray 2005,[w19] Canada	RC	Pre-eclampsia	Mixed	P	140, 90	0.3	36 982/1 026 265	8.7	Non-fatal stroke¶	415	1.9 (1.45 to 2.27)	Smoking, Socioeconomic status, gestational diabetes, obesity, dyslipidaemia, hypertension, type 2 diabetes mellitus, renal disease
Total							64 551/1 671 578**	10.4	All stroke	907		

SBP=systolic blood pressure; DBP=diastolic blood pressure; PC=prospective cohort; RC=retrospective cohort; P=primiparous. All papers adjusted for maternal age, year of birth, and hospital of delivery.
*List of variables used in individual studies to adjust for effect of pre-eclampsia on later risk of chronic disease.
†Calculated from total number of woman years.
‡Codes 430-438 from international classification of diseases, eighth revision.
§Codes 430-438 from international classification of diseases, ninth revision and, for Wilson 2003,[w14] also codes I60-I69 from 10th revision
¶ICD9 Codes 433, 434, 436, 437.0, and 437.1, 50.11, and 50.12 from international classification of diseases, ninth revision (and ICD-10 revisions).
**1 633 180 women were included in meta-analysis as 38 398 women had non-pre-eclamptic "maternal placental syndromes" (see Ray 2005[w19]).

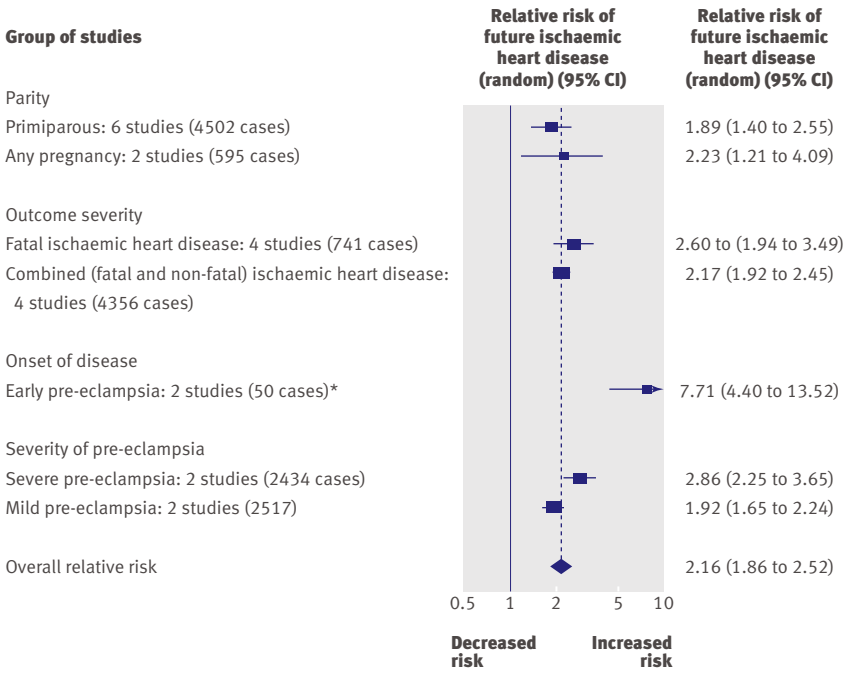

Fig 4 | Pre-eclampsia and risk of ischaemic heart disease in later life by study characteristics. *Only one study included, as data not available from Smith 2001[w16]

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 previously pregnant women) were included involving 41 084 women with pre-eclampsia and 6131 incident cancers.[w15 w17 w25] (table 6). The average weighted mean follow-up for each woman was 13.9 years, excluding one study[w25] that presented a range of follow-up rather than a mean number of 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; I^2=43.2%; fig 6) or of small study bias (Egger test, P=0.97).

Pre-eclampsia and risk of all cause mortality in later life

Four studies (794 462 women) included 49 049 with pre-eclampsia and 7537 women who later died from all causes[w13 w15-w17] (table 7). The average weighted mean follow-up was 14.5 years for each woman. 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; I^2=93.9%; fig 7) and this was most noticeable between studies of early and late pre-eclampsia (P<0.00001; I^2=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 from any cause. The major contribution to all cause mortality seems to be cardiovascular disease, as there was no difference in the relative risk of death from breast cancer or any other cancers.

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.[19] Most studies (12 of 15) only made adjustment 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 that included

Table 4 | Pre-eclampsia and risk of venous thromboembolism (VTE) in later life

Study, country	Study design	Exposures	Race	Parity	Definition of exposure: Minimum SBP, minimum DBP (mm Hg)	Definition of exposure: Minimum proteinuria g/24 h	No with pre-eclampsia/No of women	Mean follow-up (years)	No of VTE cases	Relative risk (95% CI)	Degree of adjustment*
Hannaford 1997,[w8] UK	PC	Pre-eclampsia	3	Any	140, 90	0.3	2371/17 202	12.5†	150‡	1.62 (1.09 to 2.41)	Smoking, socioeconomic status
Kestenbaum 2003,[w14] USA	RC	Mild pre-eclampsia; severe pre-eclampsia and eclampsia	3; 3	P, P	140, 90; 160, 110	0.3	15 508; 5044/113 454	7.8	141§; 126§	1.4 (0.9 to 2.2); 2.3 (1.3 to 4.2)	
Van Walraven 2003,[w20] Canada	PC	Pre-eclampsia	1	Any	140, 90	0.3	12 849/297 037	3	164§	2.2 (1.3 to 3.7)	
Total						:	35 772/427 693	4.7	470		

SBP=systolic blood pressure; DBP=diastolic blood pressure; PC=prospective cohort; RC=retrospective cohort; P=primiparous. All papers adjusted for maternal age, year of birth, and hospital of delivery.
*List of variables used in individual studies to adjust for effect of pre-eclampsia on later risk of chronic disease.
†Calculated from total number of woman years.
‡Codes 450 and 453 from international classification of diseases, ninth revision.
§Codes 415.1 and 451.1 from international classification of diseases, ninth revision.

Table 5 | Pre-eclampsia and risk of breast cancer in later life

Study, country	Study design	Exposure	Race	Parity	Definition of exposure: Minimum SBP, minimum DBP (mm Hg)	Definition of exposure: Minimum proteinuria g/24 h	No with pre-eclampsia/ No of women	Mean follow-up (years)	No of cancer cases	Relative risk (95% CI)	Degree of adjustment*
Cohn 2001,[w21] USA	PC	Pre-eclampsia	White	Any	140, 90	†	88/3804	19	146‡	1.16 (0.07 to 4.38)	
Mogren 2001,[w22] Sweden	RC	Pre-eclampsia	White	P	140, 90	0.3	3397/40 951	25	870§	1.09 (0.87 to 1.36)	
Vatten 2002,[w23] Norway	PC	Pre-eclampsia and PIH	White	P	¶, ¶	¶	42 038/694 657	16	5474**	0.81 (0.71 to 0.91	
Paltiel 2004,[w24] Israel	RC	Pre-eclampsia	Mixed	Any	140, 90	†	1070/37 033	30	978††	1.38 (1.0 to 1.89)	Parity, ethnicity, religion, type 1 diabetes mellitus
Total							46 593/776 445	17	7468		

SBP=systolic blood pressure; DBP=diastolic blood pressure; PC=prospective cohort; RC=retrospective cohort; PIH=pregnancy induced hypertension. All papers adjusted for maternal age, year of birth, and hospital of delivery.
*List of variables used in individual studies to adjust for effect of pre-eclampsia on later risk of chronic disease.
†Proteinuria (and oedema) must be present, no minimum value specified.
‡California cancer registry.
§Swedish cancer registry.
¶PIH and proteinuria as stipulated by Norwegian medical birth registry.
**Norwegian national cancer registry.
††Israeli cancer registry.

over a million women the association between pre-eclampsia and future cardiovascular disease seems to be independent of prepregnancy hypertension, diabetes mellitus, obesity, dyslipidaemia, the metabolic syndrome, and smoking.[w18] We found a similar two-fold increased risk of cardiovascular disease in those studies with incomplete adjustment for established cardiovascular risk factors.

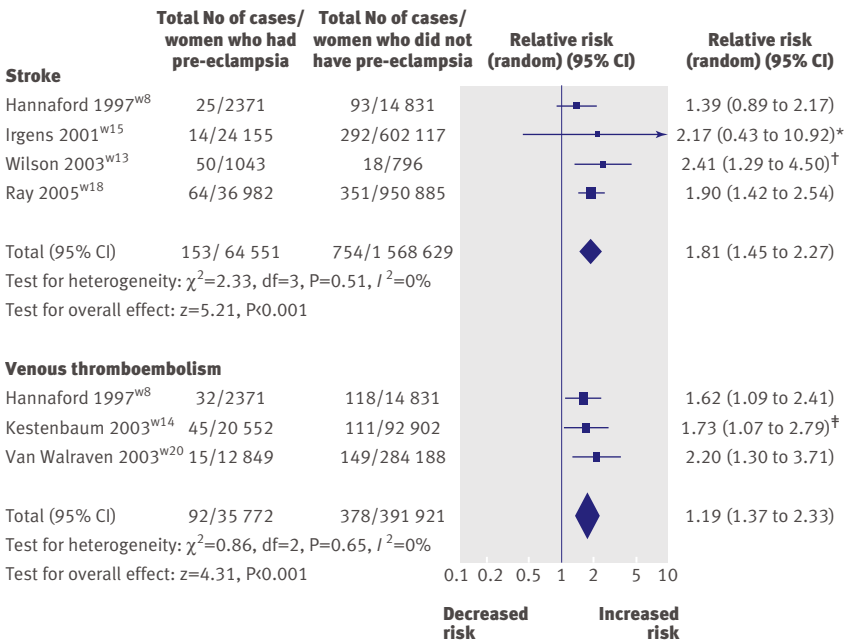

Fig 5 | Pre-eclampsia and risk of fatal and non-fatal stroke and thromboembolism in later life. *Early and later pre-eclampsia combined. †Fatal and non-fatal stroke combined. ‡Mild and severe pre-eclampsia combined

Pre-eclampsia most commonly occurs during the first pregnancy. Women who had pre-eclampsia early (<37 weeks' gestation) in their first pregnancy were more likely to have recurrent pre-eclampsia compared with those who had pre-eclampsia late in their first pregnancy (>37 weeks' gestation). Recurrent pre-eclampsia compared with a single episode has been associated with a sevenfold increased risk of later hypertension.[w3] We also 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. It is likely that women who have recurrent pre-eclampsia have an underlying pathological phenotype that puts them at risk of hypertension and cardiovascular disease.

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. It follows that the timing of onset of pre-eclampsia more accurately reflects the severity of the maternal cardiovascular phenotype than the severity to which pre-eclampsia may evolve, which more probably reflects the timeliness of antenatal observations.

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. A woman living in the United Kingdom aged 40-49 years and with an average level of risk factors for cardiovascular disease has an almost 4% risk of a cardiovascular event within 10 years (J Moon, personal communication, 2007). If the increased risk of cardiovascular disease after pre-eclampsia is independent of these risk factors this risk would increase to around 8% for an otherwise similar woman with a

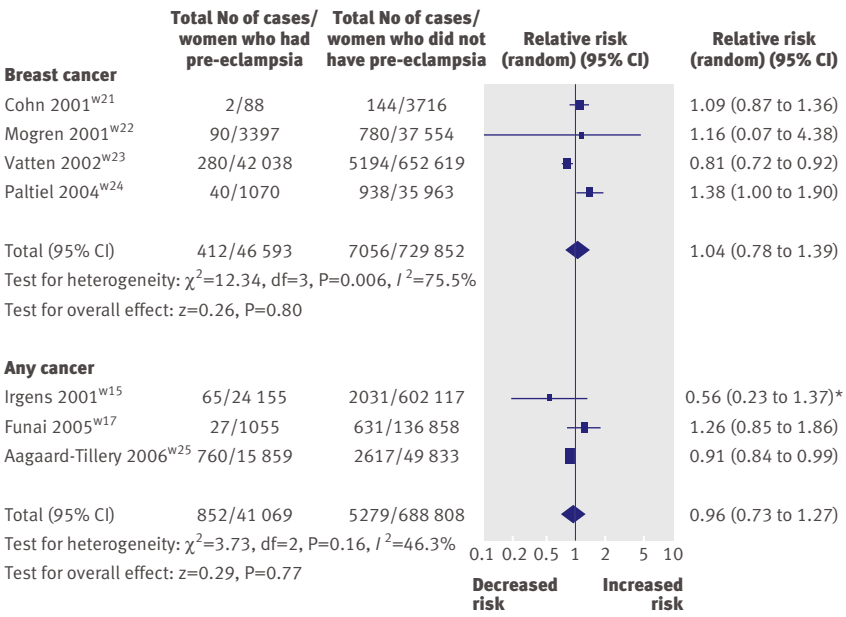

Fig 6 | Pre-eclampsia and risk of breast cancer or any cancer in later life. *Early and late pre-eclampsia combined

history of pre-eclampsia. Two reports included in our review followed up women for more than 20 years after pre-eclampsia and the data indicated that the twofold risk of later cardiovascular disease persists long term.[w13 w17] Since the risk of a cardiovascular event increases with age, absolute risk at age 50-59 years would be 8.3% and 17.8% for a woman without and with a history of pre-eclampsia and at 60-69 years would be 14.2% and 30.7%, suggesting that a woman with pre-eclampsia might become eligible for primary prevention at an earlier age.[20] The matter of the independence of the effect of pre-eclampsia on cardiovascular risk could be dealt with by an analysis of data at participant level from studies that measured risk factors.

Most populations included in the systematic review were of European origin, such as women from North America, Canada, and western Europe. It is possible that other ethnic groups will have different risk ratios for future cardiovascular disease. Women of Afro-Caribbean origin have an increased risk of pre-eclampsia,[21] which may translate into a higher risk of 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 observation 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,[1] 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.[1-23]

In support of a common causal link, obesity, hyperlipidaemia, hypertension, and other disorders associated with pre-existing endothelial dysfunction, such as diabetes mellitus and polycystic ovarian syndrome, are risk factors shared by women at risk of both pre-eclampsia and cardiovascular disease.[12] Moreover, women with inherited thrombophilias are at increased risk of pre-eclampsia and venous thromboembolic disease.[24 25] A potential role for angiogenic peptides and their endogenous inhibitors in the physiology of pre-eclampsia is in keeping with this hypothesis as these pathways have been implicated in the development of cardiovascular disease.[26] It is possible

Table 6 | Pre-eclampsia and risk of any cancer in later life

					Definition of exposure					
Study, country	Study design	Exposure	Race	Parity	Minimum SBP, minimum DBP (mm Hg)	Minimum proteinuria g/24 h	No with pre-eclampsia/ No of women	Mean follow-up (years)	Total cases cancer	Relative risk (95% CI)
Irgens 2001,[w15] Norway	RC	Pre-eclampsia 16-36 weeks; pre-eclampsia ≥37 weeks	White	P	—, 85	—	2649; 21 506/ 626 272	13	123*; 1973*	0.36 (0.12 to 1.11); 0.90 (0.29 to 2.78)
Funai 2005, [w17] Israel	RC	Pre-eclampsia	Mixed	Any	140, 90	†	1070/37 061	30	658‡	1.26 (0.85 to 1.86)
Aagaard-Tillery 2006,[w25] USA	RC	Pre-eclampsia	Mixed	Any	§, §	§	15 859/65 692	7-59	3377¶	0.91 (0.84 to 0.99)
Total							41 084/729 025	13.9**	6131	

SBP=systolic blood pressure, DBP=diastolic blood pressure; RC=retrospective cohort; P=primiparous. All papers adjusted for maternal age, year of birth, and hospital of delivery.
*Codes 140-239 from international classification of diseases, ninth revision and birth record data.
†Proteinuria (and oedema) must be present, no minimum value specified.
‡Israeli cancer registry.
§Codes 6424-6427 from international classification of diseases, ninth revision.
¶Utah cancer registry.
**Overall mean years of follow-up calculated without Aagaard-Tillery data because of presented range only.

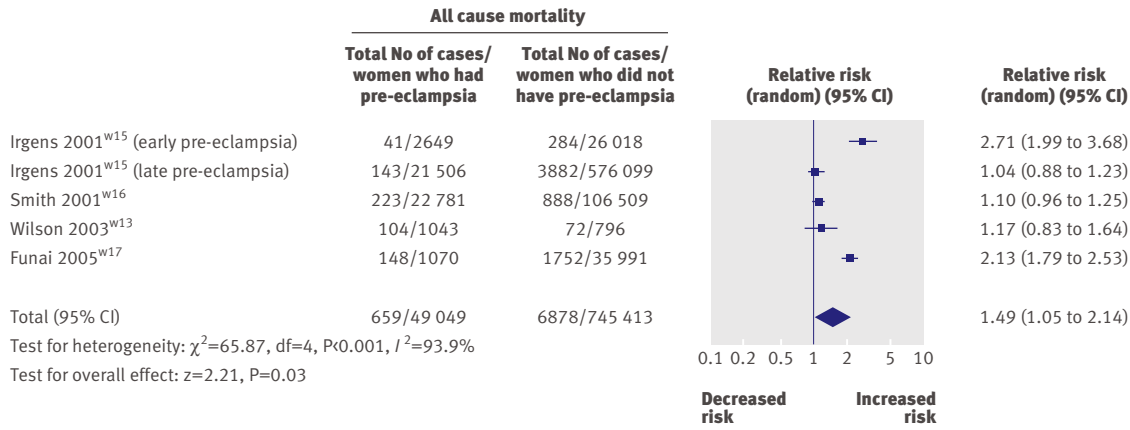

Fig 7 | Pre-eclampsia and risk of death from any cause in later life

therefore that pre-eclampsia is the initial point of expression of an inherent adverse phenotype associated with the early development of cardiovascular disease. One exception is the notable discordance between the protective effect of smoking on risk of pre-eclampsia and its deleterious effect on risk of cardiovascular disease.[27 28]

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).[29] 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 effect estimate for incident hypertension after pre-eclampsia (relative risk 3.7, 2.7 to 5.05) could be an overestimation, and a relative risk less prone to bias would be the one obtained from pooling the largest studies—that is 2.37, 2.11 to 2.66.

Assessing the quality of included studies is controversial. The application of a quantitative score of study quality as part of study selection in meta-analysis is a process that has not been validated and can itself introduce bias. To overcome this problem we evaluated relevant study characteristics that may introduce bias to the meta-analysis, and we used these characteristics in a sensitivity analysis (fig 4). This approach

Table 7 | Pre-eclampsia and risk of death from any cause in later life

Study, country	Study design	Exposure	Race	Parity	Definition of exposure: Minimum SBP, minimum DBP (mm Hg)	Definition of exposure: Minimum proteinuria g/24 h	No with pre-eclampsia/ No of women	Mean follow up (years)	No of cases	Relative risk (95% CI)	Degree of adjustment*
Irgens 2001,[w15] Norway	RC	Pre-eclampsia 16-36 weeks; pre-eclampsia ≥ 37 weeks	White	P	—, 85	—	2649; 21 506/626 272	13	325; 4025	2.71 (1.99 to 3.68); 1.04 (0.88 to 1.23)	
Smith 2001,[w16] UK	RC	Pre-eclampsia	White	P	†, †	†	22 781/129 290	16.9	1111	1.1 (0.96 to 1.25)	Socioeconomic status
Wilson 2003,[w13] UK	RC	Pre-eclampsia and eclampsia	White	P	90	0.3	1043/1839	32	176	1.17 (0.83 to 1.64)	Socioeconomic status
Funai 2005,[w17] Israel	RC	Pre-eclampsia	Mixed	Any	140, 90	‡	1070/37 061	30	1900	2.13 (1.79 to 2.53)	Socioeconomic status, type 2 diabetes, gestational diabetes
Total							49 049/794 462	14.5	7537		

SBP=systolic blood pressure; DBP=diastolic blood pressure; RC=retrospective cohort; P=primiparous. All papers adjusted for maternal age, year of birth, and hospital of delivery.
*List of variables used in individual studies to adjust for effect of pre-eclampsia on later risk of chronic disease.
†Hypertension, proteinuria or albuminuria, or both from Scottish morbidity records.
‡Proteinuria (and oedema) must be present, no minimum value specified.

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

indicated that the findings were robust. Most of the studied cohorts were retrospective, which limited our ability to assess adequately the effect of potential confounders on observed associations.

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).

The WHO criteria for international classification of diseases were universally adopted for the diagnoses of all outcomes except hypertension. A minimum diastolic blood pressure of 90 mm Hg or the use of antihypertensives after the pregnancy with pre-eclampsia were used to diagnose hypertension. As included studies spanned more than 40 years, alterations in diagnostic criteria occurred, with reclassification (eighth, ninth, and 10th revisions). This may not have affected the numbers of future events but may have increased the likelihood of misclassification. Since the overall relative risks were consistently increased for all cardiovascular outcomes, this possibility is unlikely.

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. The lack of association between pre-eclampsia and future cancer, in particular breast cancer, suggests a specific relation between pre-eclampsia and cardiovascular disease.

The mechanism underlying this association remains to be defined, but whatever its nature a history of pre-eclampsia should be considered in the evaluation of women's risk of cardiovascular disease. If the risk proves independent of established risk factors for cardiovascular disease, affected women would be eligible for preventive therapies at an earlier age than usual.

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