

Prepregnancy cardiovascular risk factors as predictors of pre-eclampsia: population based cohort study

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ABSTRACT

Objective To examine the effect of cardiovascular risk factors before pregnancy on risk of pre-eclampsia.

Design Population based prospective study.

Setting Linkage between a Norwegian population based study (Nord-Trøndelag health study, HUNT-2) and Norway's medical birth registry.

Participants 3494 women who gave birth after participating in the Nord-Trøndelag health study at baseline; of whom 133 (3.8%) delivered after a pre-eclamptic pregnancy.

Main outcome measure Odds ratio of developing pre-eclampsia.

Results After adjustment for smoking; previous pre-eclampsia; parity; maternal age, education, and socioeconomic position; and duration between baseline measurements and delivery, positive associations were found between prepregnancy serum levels of triglycerides, cholesterol, low density lipoprotein cholesterol, non-high density lipoprotein cholesterol, and blood pressure and risk of pre-eclampsia. The odds ratio of developing pre-eclampsia for women with baseline systolic blood pressures greater than 130 mm Hg (highest fifth) was 7.3 (95% confidence interval 3.1 to 17.2) compared with women with systolic blood pressures less than 111 mm Hg (lowest fifth). Similar results were found for nulliparous and parous women. Women who used oral contraceptives at baseline had half the risk of pre-eclampsia compared with never or former users (0.5, 0.3 to 0.9).

Conclusion Women with cardiovascular risk factors may be predisposed to pre-eclampsia.

INTRODUCTION

Women with pre-eclampsia have been shown to have unfavourable cardiovascular risk profiles in pregnancy, associated with levels of serum lipids, body mass, and blood pressure.¹⁻⁴ It remains uncertain if these characteristics reflect primary causes of pre-eclampsia or are secondary markers of the disease process. It is also uncertain whether the increased risk of cardiovascular disease is due to exposures during a pre-eclamptic pregnancy or due to underlying biological traits of the mother.

We prospectively examined whether cardiovascular risk factors before pregnancy can predict pre-eclampsia.

METHODS

All residents of Nord Trøndelag County in Norway aged 20 years or more were invited to participate in the Nord-Trøndelag health study (HUNT-2) between 1995 and 1997.⁵ The study includes data on height, weight, waist circumference, blood pressure, and non-fasting serum

lipids and glucose levels in 66 140 adults. A questionnaire provided details on medical and lifestyle factors, including history of diabetes and cardiovascular disease, smoking, and education. Social position was evaluated from self reported employment status and whether women received social security benefits. To obtain information on births from 1995 to March 2005 we linked the participating women to Norway's medical birth registry. We identified 4251 women giving birth at least nine months after the baseline study. After exclusions (see bmj.com) data on 3494 women were available for analysis; 133 (3.8%) of these women had a pre-eclamptic pregnancy. We also investigated the influence of a family history of cardiovascular diseases and diabetes on risk of pre-eclampsia.

Norway's medical birth registry contains information on maternal health before and during pregnancy, complications in pregnancy, and the fetus.⁶ Pre-eclampsia is routinely entered, defined as a sustained increase in blood pressure to at least 140/90 mm Hg after mid-gestation combined with proteinuria of at least + or more. Hypertension and proteinuria should be apparent on two occasions at least 4-6 hours apart.⁷

Trained staff measured blood pressure three times at intervals of one minute. We used the mean of the second and third reading in this study.

Blood sampling was done in the non-fasting state, and we analysed serum concentrations of total cholesterol, high density lipoprotein cholesterol, triglycerides, and glucose after sampling (see bmj.com).⁵ We calculated low density lipoprotein cholesterol levels in participants only with triglyceride concentrations less than 4.5 mmol/l. We also calculated non-high density lipoprotein cholesterol levels as the difference between levels of total serum cholesterol and high density lipoprotein cholesterol. Staff recorded height, weight, body mass index, and waist circumference.⁵

Statistical analysis

We used logistic regression analysis to estimate crude and adjusted associations of cardiovascular risk factors with risk of pre-eclampsia. In the adjusted analyses we controlled for the interval from baseline measurements (Nord-Trøndelag health study) to the index birth, maternal age, parity, previous pre-eclampsia, smoking, educational level, and whether the women received social security benefits. In the analyses of lipids we also adjusted for time since last meal. To avoid the influence of a previous pregnancy, we also stratified by parity to examine whether the associations differed between nulliparous and parous women. We separately studied associations with early onset pre-eclampsia by using

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pre-eclampsia with preterm delivery as a diagnostic indicator.

RESULTS

The mean age at baseline in the Nord-Trøndelag health study was 25.4 years for women who developed pre-eclampsia and 26.7 years for women who did not (see [bmj.com](#)). Time from baseline to delivery was almost similar between the groups. Women with diabetes, chronic hypertension, or previous pre-eclampsia were over-represented in the pre-eclampsia group, and the proportion of nulliparous women was also higher (64% *v* 42%). Women with preterm delivery and those who delivered a small for gestational age infant were more likely to have a diagnosis of pre-eclampsia.

Women who were former and current smokers had a lower risk of pre-eclampsia than women who did not smoke (see [bmj.com](#)), and women who received social security benefits seemed to be at higher risk than those who did not receive benefits. Women with more than 14 years' education had a 70% (95% confidence interval

20% to 90%) lower risk of pre-eclampsia than women with less than 9 years' education. Women who used oral contraceptives at baseline had nearly half the risk of pre-eclampsia of never or former users (adjusted odds ratio 0.6, 95% confidence interval 0.3 to 1.0). Family history of cerebrovascular disease showed no association, but hypertension, ischaemic heart disease, and diabetes were each associated with a doubling in risk (see [bmj.com](#)).

A strong positive association was found between pre-pregnancy systolic and diastolic blood pressure and pre-eclampsia (table 1). After multivariable adjustment, the odds ratio for women with a baseline systolic blood pressure greater than 130 mm Hg was 7.3 (95% confidence interval 3.1 to 17.2) compared with women with a systolic blood pressure less than 111 mm Hg. Similarly, the odds ratio for women with a diastolic blood pressure greater than 78 mm Hg was 6.3 (2.9 to 14.6) compared with women with a diastolic pressure less than 64 mm Hg. Additional adjustment for prepregnancy body mass index did not influence these associations. Overweight

Table 1 | Odds ratio for pre-eclampsia according to fifths of prepregnancy systolic and diastolic blood pressure, body mass index, waist circumference, and height

Variables (fifths)	Women with pre-eclampsia/ women without pre-eclampsia*	Odds ratio (95% CI)		P for trend
		Crude estimate	Adjusted estimate†	
Systolic blood pressure (mm Hg):				
<111	6/664	1.0 (reference)	1.0 (reference)	
111-116	13/672	2.1 (0.8 to 5.7)	2.1 (0.8 to 5.5)	
117-121	27/611	4.9 (2.1 to 11.9)	4.3 (1.8 to 10.6)	<0.001
122-129	32/739	4.8 (1.9 to 11.5)	4.1 (1.7 to 9.9)	
≥130	55/675	9.0 (3.9 to 21.1)	7.3 (3.1 to 17.2)	
Diastolic blood pressure (mm Hg):				
<64	7/637	1.0 (reference)	1.0 (reference)	
64-67	12/587	1.8 (0.7 to 4.7)	1.9 (0.7 to 4.9)	
68-71	30/663	4.1 (1.8 to 9.4)	4.3 (1.9 to 9.9)	<0.001
72-77	34/788	3.9 (1.7 to 8.8)	3.7 (1.6 to 8.5)	
≥78	50/686	6.6 (3.0 to 14.7)	6.5 (2.9 to 14.6)	
Body mass index:				
<21.23	20/669	1.0 (reference)	1.0 (reference)	
21.23-22.80	18/686	0.9 (0.5 to 1.7)	0.9 (0.5 to 1.8)	
22.81-24.53	25/672	1.2 (0.7 to 2.3)	1.3 (0.7 to 2.3)	0.02
24.54-27.07	35/662	1.8 (1.0 to 3.1)	1.9 (1.1 to 3.4)	
≥27.08	34/663	1.7 (1.0 to 3.0)	1.9 (1.1 to 3.4)	
Waist circumference (cm):				
<67	22/694	1.0 (reference)	1.0 (reference)	
68-71	25/693	1.1 (0.6 to 2.0)	1.2 (0.7 to 2.2)	
72-76	24/743	1.0 (0.6 to 1.8)	1.2 (0.7 to 2.2)	<0.001
77-82	26/571	1.4 (0.8 to 2.6)	1.7 (1.0 to 3.1)	
≥83	36/654	1.7 (1.0 to 3.0)	2.2 (1.2 to 3.8)	
Height (cm):				
<162	34/805	1.0 (reference)	1.0 (reference)	
163-165	21/645	0.8 (0.4 to 1.3)	0.8 (0.5 to 1.4)	
166-168	33/677	1.1 (0.7 to 1.9)	1.2 (0.7 to 2.0)	0.6
169-171	19/561	0.8 (0.5 to 1.4)	0.9 (0.5 to 1.5)	
≥172	26/669	0.9 (0.5 to 1.5)	0.9 (0.6 to 1.6)	

*Some variation in number of women without pre-eclampsia owing to missing data.

†Adjusted for maternal age at birth, duration between baseline study and index delivery, education, parity, previous pre-eclampsia, receiving social security benefits, and smoking.

and obese women had a higher risk of pre-eclampsia than women of normal weight and, similarly, the risk for pre-eclampsia increased with increasing waist circumference. Maternal height had no effect.

Positive associations were found between prepregnancy serum levels of triglycerides, total cholesterol, and low density lipoprotein cholesterol and risk of pre-eclampsia (table 2). The risk increased with increasing levels. Unfavourable levels of high density lipoprotein cholesterol and glucose were also associated with an

increased risk of pre-eclampsia, but these associations were not as robust.

The results of an association between cardiovascular risk factors and pre-eclampsia in nulliparous women were similar to the overall results but showed slightly stronger associations for triglycerides (see [bmj.com](#)). When cases of pre-eclampsia were restricted to women with early onset or late onset disease, no differences were found (see [bmj.com](#)).

DISCUSSION

Unfavourable cardiovascular risk factors before pregnancy are strong predictors of pre-eclampsia. Prepregnancy systolic and diastolic blood pressure showed linear associations with risk for pre-eclampsia, and the positive associations with levels of serum lipids (cholesterol, low density lipoprotein cholesterol, and triglycerides) were associated with particularly high risk among women with levels above the normal range.

The prospective design and population base of this study make bias an unlikely explanation for the results. A limitation of this study, however, could be sampling blood in the non-fasting state. Triglyceride concentrations are sensitive to recent food intake, but cholesterol levels seem to be less influenced.⁸ We tried to overcome this problem by adjusting for time since last meal; this did not alter the results. Our findings are likely to have been conservatively estimated, however, because non-differential measurement error will have occurred.

Pre-eclampsia can be misclassified, and we cannot exclude this possibility in our study. If women with high blood pressure before pregnancy are, at a given level of blood pressure and proteinuria, more likely to have a diagnosis of pre-eclampsia during pregnancy this would generate a bias that would strengthen the association between prepregnancy blood pressure and pre-eclampsia. This could plausibly happen if surveillance for pre-eclampsia was greater among women with high blood pressure before pregnancy. This would not generally be known, however, and only six women had prepregnancy blood pressures consistent with hypertension. Therefore we feel that this potential source of bias is unlikely to substantially influence our results.

The association between cardiovascular disease and diabetes in a first degree relative that we observed is in agreement with others.⁹⁻¹¹ Unlike other studies,^{9,10} we found no association with family history of cerebrovascular disease.

Several studies have indicated that the risk of pre-eclampsia is lower in women who smoke than in those who do not, but the mechanism is not fully understood.¹² Women who develop pre-eclampsia and smoke seem to have a poorer outcome than those who do not smoke.¹³ This may indicate a synergy between smoking and pre-eclampsia or that smoking masks the symptoms of pre-eclampsia.

The negative association found with use of oral contraceptives at baseline is difficult to explain. Contrary to our results, another study reported an increased risk of pre-eclampsia and a reduced risk of gestational hypertension among women who used oral contraceptives.¹⁴ It is

Table 2 | Odds ratio for pre-eclampsia according to prepregnancy lipid and glucose levels

Variables (fifths)	Women with pre-eclampsia/ women without pre-eclampsia*	Odds ratio (95% CI)		P for trend
		Crude estimate	Adjusted estimate†	
Triglycerides (mmol/l):				
<0.70	21/653	1.0 (reference)	1.0 (reference)	0.11
0.70-0.90	25/688	1.1 (0.6 to 2.0)	1.1 (0.6 to 2.0)	
0.91-1.13	25/679	1.1 (0.6 to 2.1)	1.0 (0.6 to 1.9)	
1.14-1.53	23/673	1.1 (0.6 to 1.9)	1.0 (0.5 to 1.8)	
≥1.54	38/661	1.8 (1.0 to 3.1)	1.6 (0.9 to 2.9)	
Cholesterol (mmol/l):				
<4.1	17/567	1.0 (reference)	1.0 (reference)	0.03
4.1-4.5	26/676	1.3 (0.7 to 2.4)	1.3 (0.7 to 2.4)	
4.6-4.9	22/679	1.1 (0.6 to 2.1)	1.0 (0.5 to 2.0)	
5.0-5.5	27/767	1.2 (0.6 to 2.2)	1.2 (0.6 to 2.3)	
≥5.6	40/665	2.0 (1.1 to 3.6)	2.1 (1.2 to 3.8)	
HDL cholesterol (mmol/l):				
<1.2	21/515	1.1 (0.7 to 2.0)	1.3 (0.8 to 2.4)	0.13
1.21-1.39	33/770	1.2 (0.7 to 1.9)	1.3 (0.8 to 2.2)	
1.40-1.49	17/408	1.2 (0.6 to 2.1)	1.3 (0.7 to 2.5)	
1.50-1.69	27/710	1.1 (0.6 to 1.8)	1.1 (0.6 to 1.8)	
≥1.7	34/951	1.0 (reference)	1.0 (reference)	
LDL cholesterol (mmol/l):				
<2.47	19/681	1.0 (reference)	1.0 (reference)	0.005
2.48-2.90	27/668	1.4 (0.8 to 2.6)	1.4 (0.8 to 2.6)	
2.91-3.31	26/671	1.4 (0.8 to 2.5)	1.4 (0.7 to 2.5)	
3.32-3.81	21/675	1.1 (0.6 to 2.1)	1.1 (0.6 to 2.1)	
≥3.82	39/653	2.1 (1.2 to 3.7)	2.4 (1.3 to 4.3)	
Non-HDL cholesterol (mmol/l):				
<0.91	18/678	1.0 (reference)	1.0 (reference)	0.002
0.92-1.39	27/669	1.5 (0.8 to 2.8)	1.7 (0.9 to 3.2)	
1.40-1.87	28/668	1.6 (0.9 to 2.9)	1.6 (0.9 to 3.0)	
1.88-2.42	20/676	1.1 (0.6 to 2.1)	1.2 (0.6 to 2.3)	
≥2.43	39/657	2.2 (1.3 to 4.0)	2.7 (1.5 to 5.0)	
Glucose (mmol/l):				
<4.4	20/649	1.0 (reference)	1.0 (reference)	0.15
4.4-4.6	25/630	1.3 (0.7 to 2.4)	1.4 (0.8 to 2.6)	
4.7-4.8	20/522	1.2 (0.7 to 2.3)	1.3 (0.7 to 2.6)	
4.9-5.2	36/782	1.5 (0.9 to 2.6)	1.6 (0.9 to 2.8)	
≥5.3	31/771	1.3 (0.7 to 2.3)	1.3 (0.7 to 2.3)	

HDL=high density lipoprotein; LDL=low density lipoprotein.

*Some variation in number of women without pre-eclampsia owing to missing data, and data are missing on lipid and glucose levels in one woman with pre-eclampsia.

†Adjusted for maternal age at birth, duration between the baseline study and index delivery, education, parity, previous pre-eclampsia, smoking, receiving social security benefits, and time since last meal.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Women with previous pre-eclampsia are at increased risk of cardiovascular diseases
 Women with pre-eclampsia have unfavourable metabolic profiles in pregnancy

WHAT THIS STUDY ADDS

Cardiovascular risk factors that are present years before pregnancy are associated with a risk of pre-eclampsia

possible that screening for thromboembolic conditions and a family history of cardiovascular diseases among users of oral contraceptives could have resulted in the selection of women less prone to cardiovascular disease among baseline users of oral contraceptives in our study. However, we found no differences in cardiovascular risk factors between users, former users, and never users of oral contraceptives at baseline. We also used time until pregnancy as a proxy variable for fertility, and examined whether time to pregnancy could have confounded the results. We found no association between this proxy and risk of pre-eclampsia. Since a long interval between pregnancies increases the risk of pre-eclampsia,¹⁵ we also restricted the analysis to nulliparous women, but the negative association with use of oral contraceptives at baseline persisted.

Several studies have suggested that early and late onset pre-eclampsia, may have different causes,¹⁶⁻¹⁸ whereas others suggest that the risk profiles are similar.¹⁹ Our results support similarity, since the associations with cardiovascular risk factors showed similar patterns for both early onset (≤ 36 weeks) and late onset pre-eclampsia (≥ 37 weeks).

The excessive metabolic changes of pre-eclamptic pregnancies may be regarded as a stress test for maternal cardiovascular function.²⁰ Several studies have linked pre-eclampsia with higher risk of future cardiovascular disease of the mother,²¹⁻²³ suggesting that pre-eclampsia and cardiovascular diseases may share common pathophysiological mechanisms.¹² The pathogenesis of pre-eclampsia is uncertain, but predisposition to endothelial dysfunction is thought to play a crucial part.^{16 24 25} Risk factors for pre-eclampsia such as chronic hypertension share the feature of endothelial dysfunction.¹¹⁶ Furthermore, unfavourable lipid levels are associated with endothelial dysfunction and may precede the development of atherosclerotic disease.²⁶ Studies have also shown acute atherosclerosis in vessels of the placenta bed in pre-eclamptic women.²⁷

In conclusion, we found that cardiovascular risk factors that were present years before pregnancy are associated with a risk of pre-eclampsia. This does not, however, rule out the possibility that pre-eclampsia in itself may contribute to cardiovascular risk.

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Competing interests: None declared.

Ethical approval: This study was approved by regional science ethics committees in Norway and the medical birth registry of Norway.

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