The non-traditional and familial risk factors for preeclampsia in the FINNPEC cohort

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Abstract

Background Considering the burden of preeclampsia (PE), it is important to understand better the underlying risk factors involved in its etiology. In this nationwide study, we studied the association of background factors with PE with an emphasis on socioeconomic factors, reproductive factors and health history enclosing the parents of pregnant women.

Methods In the Finnish Genetics of Pre-eclampsia Consortium (FINNPEC) cohort participants filled in a questionnaire on background information including data on socioeconomic factors, health history and reproductive factors. The questionnaire data was available from 708 women with PE and 724 control women. Two different control groups, healthy controls with uncomplicated pregnancies (n=498) and all controls (n=724, including controls with uncomplicated pregnancies and pregnancy complications other than PE), were established. Background information among PE women and the two different control groups were compared.

Results PE women had similar socioeconomic status and more often non-communicable diseases including type I diabetes, chronic hypertension and hyperlipidemia than the two control groups ($p<0.05$ for all). Depression was more common among PE women (11.4%) than among all controls (7.6%) ($p=0.019$). Subfertility (estimated by time to pregnancy) was more common among PE women ($p=0.013$ for healthy controls, $p=0.019$ for all controls). PE women had earlier menarche ($p=0.001$ for healthy controls, $p=0.022$ for all controls). Hypertension was more common in both parents of PE women ($p<0.001$), stroke in fathers (PE women 6.2 %, healthy controls 3.2 % ($p=0.020$) and all controls 3.5 % ($p=0.022$)) and diabetes in mothers (PE women 7.5 %, healthy controls 3.1 % ($p=0.001$) and all controls 4.3 % ($p=0.012$)). Mental disorders including depression were more common in mothers of PE women compared to controls (PE women 7.2 %, healthy controls 3.7 % ($p=0.013$) and all controls 3.9 % ($p=0.007$)).

Conclusions In this Finnish nationwide FINNPEC cohort, PE women had similar socioeconomic status, more non-communicable diseases and depression, earlier menarche, more subfertility and more parental non-communicable diseases compared to controls. As a novel finding we found more mental disorders including depression in mothers of PE women.

Background

Preeclampsia (PE) is a pregnancy complication characterized by coexistence of hypertension and one or more of the following new-onset conditions: proteinuria, other maternal organ dysfunction or uteroplacental dysfunction (1). It affects 3–5 % of pregnancies and is a major cause of maternal, fetal and neonatal mortality and morbidity (2). The etiology of PE remains unclear but reduced placental perfusion and inflammation associating with oxidative stress and endothelial dysfunction are considered as central features in its pathogenesis. Maternal genetic, behavioral and metabolic factors are thought to contribute to the PE phenotype (3). Several maternal risk factors for PE have been identified such as previous PE, chronic hypertension, pregestational diabetes, body mass index (BMI) > 30 kg/m², use of assisted reproductive technology (ART), chronic kidney disease, antiphospholipid syndrome and other autoimmune disorders (2,4). However, known clinical risk factors are predictive only in 30 % of PE women (2).

The information on other characteristics or exposures as risk factors for PE is inconsistent and/or modest. Low socioeconomic status is associated with PE in most (5–8) but not all studies (9,10). Previously only few studies have assessed the association with childhood socioeconomic status and PE (10,11). An increasing amount of studies have investigated the association between PE and use of medication. In a systematic review antidepressant use during the second trimester was associated with an increased risk of PE (12). Whether antidepressants or underlying depression affect the risk of PE independently remains uncertain, because depression itself is related to PE (13,14). Family history of hypertension and cardiovascular disease (CVD) have been shown to increase risk for PE (15) but to our knowledge, family history of depression has not been studied. Few studies have addressed the association of age at menarche with the risk of PE and the results have been conflicting. Early age at menarche has been associated with PE in a few (16,17) but not all studies (18).

Identifying women at risk for PE is important in early pregnancy because strategies to prevent PE are available. Aspirin initiated at ≤ 14 weeks of gestation reduces the risk of preterm PE in women with high risk for PE (19). Since traditional risk factors predict only 30 % of women who develop PE later in pregnancy, we focused on less explored risk factors: socioeconomic factors, health history including the parents of the study participants and reproductive factors. (2).

Methods

Study design

Data was derived from the prospective arm of the Finnish Genetics of Pre-eclampsia Consortium (FINNPEC) cohort. FINNPEC, a cross-sectional case-control multicentre study, was established to set up a nationwide clinical and DNA database on women with and without PE including their partners and infants in order to identify genetic risk factors for PE. Details of the study design, methods and procedures have been described in the FINNPEC cohort profile (20).

Study subjects

In the current study, we included 923 women with PE and 1009 controls recruited during 2008–2011. The inclusion criteria were age above 18 years, a singleton pregnancy and ability to provide an informed consent based on information in Finnish or Swedish. Using the American College of Obstetricians and Gynecologists (ACOG) 2002 criteria, PE was defined as hypertension and proteinuria (21). Hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg after 20 weeks of gestation. Proteinuria was defined as the urinary excretion of ≥0.3 g protein in a 24-hour specimen, or 0.3g/l, or two ≥1+ readings on dipstick in a random urine sample with no evidence of a urinary tract infection. Each diagnosis was confirmed independently from medical records by a research nurse and a research physician. The FINNPEC study protocol was approved by the coordinating Ethics Committee of the Hospital District of Helsinki and Uusimaa.

The participants were asked to fill a detailed questionnaire on background information including data on socioeconomic factors, health history and reproductive factors. Information on pre-pregnancy weight and height, obstetric history, pregnancy outcome, delivery and newborn was obtained from the hospital records and maternity cards. Data on smoking were collected from the maternity cards and complemented from the background information questionnaires. The participants filled in the questionnaire during pregnancy, or shortly after delivery.

A detailed questionnaire on background information was available from 708 women with PE (76.7 %) and 724 control women (71.8 %). Two different control groups were established for the current study. A subgroup of *healthy controls* consisted of 498 healthy women with uncomplicated pregnancies. *All controls* (n = 724) included also women with other pregnancy complications than PE.

Statistical analysis

Statistical analyses were performed using SPSS Statistics 23.0 (IBM Corp., Armonk, NY, USA). Background information among PE women and the two different control groups were compared separately (PE vs. healthy controls and PE vs. all controls). The normality of distributions was verified graphically and with the Kolmogorov-Smirnov-test. Statistical analyses of continuous variables were performed using the two-sample t-test for normal and Mann–Whitney U-test for skewed distributions. For categorical variables comparisons between the groups were performed with the Chi-square test. *P* value of <0.05 was considered as statistically significant.

Results

Basic characteristics of the study population

Basic characteristics of the study participants are presented in Table 1. Women with PE were more often nulliparous and had a higher BMI than women in the two control groups. They delivered earlier and more often with a caesarean section. PE women who did not respond to the questionnaire were more often multiparous, had a higher BMI and delivered earlier and more often with a caesarean section compared to responding PE women. There were no differences in the background factors between the respondents and non-respondents in the control groups (data not shown).

Socioeconomic factors

Socioeconomic factors of the study participants are presented in Table 2. Women with PE were more often employed and they worked more hours/week than women in the two control groups. However, when the women without employment (including housewives, students and unemployed) were excluded, there was no difference in the weekly working hours between the groups. PE women reported more unemployment during the 12 months preceding delivery. Women in the control groups were more often housewives and married.

There were no differences in education level, income and area of residence between the PE women and controls.

Health history

Information on the participants' health and pregnancies is shown in Table 3. The subjective health of the women suffering from PE was poorer. PE women had more often pre-existing medical conditions (Table 4) including type I diabetes, chronic hypertension, hyperlipidemia and depression. The use of any regular or seasonal medication did not differ between women with PE and all controls (Table 5). When compared to healthy controls, women with PE used more often selective serotonin reuptake inhibitors (SSRIs) and metformin. Women with PE were more often on insulin and antihypertensive medication, including medications used before pregnancy, than women in the two control groups. Reported oral health was found similar between women with PE and all controls. However, women with PE were more often treated for tooth decay than the healthy controls (data not shown).

Reproductive factors

Menarche occurred earlier in the women with PE compared to the control groups (Table 3). It took more time to conceive for women with PE, more than twelve months for 16.7 % of women with PE, for 12.4 % of healthy controls and for 12.8 % of all controls. The use of ART did not differ between the groups.

Study participants' parents

Education and medical history of the index patient's family is presented in Table 6. The fathers of the women in the control groups had higher education than those of the women with PE, whereas there were no differences regarding the education of the participants' mothers. Both parents of PE women suffered more often from hypertension than the parents of the women in the two control groups. Also stroke was more prevalent in the fathers of the women with PE. Diabetes and mental disorders, including depression, were more common in mothers of PE women. Furthermore, PE women were more often born from a pregnancy complicated by PE than the women in the control groups.

Discussion

In this Finnish nationwide FINNPEC cohort, women with PE had similar socioeconomic status, more non-communicable diseases and depression, earlier menarche and more subfertility compared to controls. Hypertension was more common in both parents, stroke in fathers and diabetes and mental disorders including depression in mothers of PE women compared to controls.

The socioeconomic status of the study groups was similar estimated both by education and income which is in line with some previous studies (9,10). In contrast, several previous studies have reported an association between low socioeconomic status and PE (5–8) when maternal education (5,6) or income (7,8) have been

used as indicators of socioeconomic status. It remains unclear whether the association between PE and low socioeconomic status found in some studies is attributed to inadequate prenatal care or to low socioeconomic status itself. Inadequate prenatal care is associated with PE, and women with low socioeconomic status are less likely to receive adequate prenatal care (7). In Finland services of the maternity clinics are free of charge and of high-quality and used by more than 90 % of pregnant women. Thus, inadequate prenatal care is not likely to be an intermediating factor in our population. Furthermore, in Finland there are fairly small differences between social classes and education is costless also at university level.

Only few studies have explored the association between socioeconomic status in childhood and adulthood and hypertensive pregnancy disorders. Studies carried out in Sweden and in the UK found that neither childhood nor adulthood socioeconomic status were related to PE (10,11). In our study there was no difference in the socioeconomic status regarding mothers of the study participants, but the fathers of the women in the control groups had a higher education level. The results are not completely comparable with previous studies which used both education, family social class (11) and childhood social class based on occupation of study participants' fathers (10) as indicators of socioeconomic status.

We found that women with PE were more often employed than the women in the control groups. Yet there was more unemployment among PE women during the last 12 months. This is probably due to the fact that women in the control groups were more often multiparous and housewives. Among employed women, the weekly working hours did not differ between the groups, in line with previous studies (22,23). A Dutch cohort study found no difference in the risk of PE between employed and unemployed women. They also compared the risk of PE among women experiencing different types of unemployment and reported that housewives and job-seeking women had a similar risk of PE as employed women. However, when compared to housewives, job-seeking women had a higher risk for PE. (23) The discrepancy with our results may be partly due to a smaller number of PE women in the Dutch cohort. In addition, the population of the Dutch study was somewhat different concerning employment. The percentage of all employed women was 72 % in the Dutch study compared to 66.8 % for PE women, 54.3 % for healthy controls and 56.3 % for all controls in the present study.

Our data suggest that the overall health was worse in the women developing PE compared to the control women. The known clinical risk factors for PE such as pregestational diabetes, chronic hypertension and hyperlipidemia were more prevalent also in this study population (2,4,24).

Our finding on increased incidence of depression among women with PE is in line with the results of two meta-analyses (13,14) which showed that both a history of depression and depressive symptoms during pregnancy are associated with an increased risk of PE. Depression and PE may share common pathophysiologic pathways since inflammation and oxidative stress are associated both with depression and PE (3,25). The use of SSRIs was higher among women with PE than controls with uncomplicated pregnancy, but there were no differences when the women with PE were compared to all controls. A systematic review of seven studies showed that the use of antidepressants during the second trimester of pregnancy was associated with a modestly increased risk of PE or gestational hypertension (12). The risk of PE appeared to be low in patients using SSRIs or serotonin-norepinephrine reuptake inhibitors and remains

inconclusive in patients using tricyclic antidepressants. The data on the association of antidepressive medication and PE are inconsistent (12). Recently, Lupattelli et al. reported that SSRI use in early and midpregnancy did not increase the risk of late-onset PE (26). De Oecampo et al. showed that women who continued to use antidepressants of two or more classes during the second half of pregnancy had increased risk for PE, whereas the use of any single antidepressant was not connected to increased risk for PE (27). It remains unclear whether depression itself or the antidepressive medication independently relate to PE. Further research is needed to indicate whether there is an association between antidepressant use during pregnancy and the development of PE.

The parents of PE patients had more morbidity compared to those of the controls' including hypertension which is in line with some previous studies (15,28,29). Family history of CVDs including stroke (15,29) and type II diabetes (30) have been shown to increase risk of PE. Our findings on fathers of the PE women suffering from stroke and mothers with diabetes are in accordance with previous data. We also found an increased incidence of mental disorders including depression among PE womens' mothers. To our knowledge there is no previous published research on this topic.

Earlier menarche in women with PE compared to the women in control groups is in line with some previous studies (16,17). Higher BMI may partly mediate this association (17). Early age at menarche has been associated to gestational diabetes (31) and CVD (32). Gestational diabetes (33) and future cardiovascular morbidity (34) have been shown to be associated with PE as well. In our study women with PE had more often risk factors for metabolic syndrome, like higher BMI, which also associates with earlier menarche. This may partly explain our finding on earlier menarche with PE women. In a recent study Petry et al. found a negative association between age at menarche and subsequent blood pressure in pregnancy, but not independently with the risk of PE (35). Their results were attenuated byincreased BMI and insulin resistance. The researchers suggested that the associations between blood pressure and age at menarche are mediated by obesity and/or insulin resistance. Alternatively, there may be a common pathophysiological mechanism like systemic inflammation that links age at menarche to each of these metabolic risk factors (35). Indeed, a negative correlation between age at menarche and circulating C-reactive protein concentrations has been reported suggesting a link between early age at menarche and inflammation (36). Insulin resistance and increased blood pressure may result from low grade systemic inflammation occurring as a result of increased macrophage infiltration of adipose tissue (35). CVD is also associated with systemic inflammation with adipose tissue being a significant contributor to the inflammatory state (37). The associations between PE, early age at menarche, insulin resistance and CVD may be explained by obesity or systemic inflammation or both. Future studies are needed to better understand these associations.

Although infertility treatments were as frequent in all groups, conceiving took more time for women with PE. In line with our findings, previous studies have shown that subfertile women are at increased risk for PE (38–42). It is well recognised that pregnancies following ART are at higher risk for PE when compared with those after natural conception (43–45). Similar underlying causes may be behind PE and infertility. Hayashi et al. found that adverse obstetric outcomes in singleton pregnancies after ART may be related to maternal factors associated with infertility rather than the type of ART used (46). Inflammation and/or obesity have been

suggested as possible mechanisms linking subfertility with PE (47). These conditions may also associate PE with early age at menarche, CVD and insulin resistance.

Strengths and limitations

The main strength of this study is a nationwide and population based cohort with detailed information from medical records. Further, background information was collected on a wide basis comprising health, lifestyle and health history of the parents of the pregnant women. The response rates to the study's questionnaires were good (PE women 76.7 % and control women 71.8 %) considering that a response rate of 60 % has face validity as a measure of survey quality (48). On the other hand PE nonrespondents differed somewhat from PE respondents and this may have biased some results of the study.Information gained through questionnaires is subjective, which can be considered a limitation of this study. The completeness and accuracy of information varies from case to case.

Conclusions

In this Finnish nationwide FINNPEC cohort, PE women had similar socioeconomic status, more non-communicable diseases and depression, earlier menarche, more subfertility and more parental non-communicable diseases compared to controls. As a novel finding we found more mental disorders including depression in mothers of PE women. More attention should be paid to depression/depressive symptoms and family health history of depression in addition to somatic diseases in antenatal care.

Abbreviations

PE: Preeclampsia

FINNPEC: The Finnish Genetics of Pre-eclampsia Consortium

BMI: Body mass index

ART: Assisted reproductive technology

CVD: Cardiovascular disease

ACOG: The American College of Obstetricians and Gynecologists

SSRI: Selective serotonin reuptake inhibitor

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Declarations

Ethics approval and consent to participate

The FINNPEC study protocol was approved by the coordinating Ethics Committee of the Hospital District of Helsinki and Uusimaa. All participants signed a written informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Availability of data and materials

The authors confirm that some access restrictions apply to the data. The researchers interested in using the data must obtain approval from the FINNPEC Board (steering committee). The researchers using the data are required to follow the terms of a number of clauses designed to ensure the protection of privacy and compliance with relevant Finnish laws. Data requests may be subject to further review by the Ethics Committee and may also be subject to individual participant consent.

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Authors’ contributions

NJ, TJ, HL and EE designed the research. NJ analyzed the data and wrote the first draft of the manuscript. TJ, HL and EE contributed to the data analysis and interpretation and revised the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1. Basic maternal characteristics

	Preeclampsia (n=708)		Healthy controls (n=498)			All controls (n=724)		
	N	% or median (range)	N	% or median (range)	*p* value	N	% or median (range)	*p* value
Age at delivery	(n=707)	29.9 (5.6) [a]		29.7 (5.2) [a]	0.596	(n=721)	29.9 (5.1) [a]	0.887
Nulliparous	535 (n=707)	75.7	263	52.8	**<0.001**	404 (n=721)	56.0	**<0.001**
BMI, kg/m^2 (self-reported, pre-pregnancy)	(n=707)	24.0 (16.2-47.3)		22.7 (17.0-38.4)	**<0.001**	(n=721)	23.1 (17.0-47.4)	**<0.001**
Smoking before pregnancy	208 (n=696)	29.9	137 (n=487)	28.1	0.514	209 (n=708)	29.5	0.881
Smoking during pregnancy	63 (n=700)	9.0	58 (n=497)	11.7	0.131	85 (n=720)	11.8	0.084
Mode of delivery	(n=707)				**<0.001**	(n=723)		**<0.001**
Vaginal	426	60.3	440	88.4		614	84.9	
Caesarean section	281	39.7	58	11.6		109	15.1	
Gestational weeks at delivery	(n=707)	38 (24-42)		40 (36-43)	**<0.001**	(n=723)	40 (23-43)	**<0.001**

[a] mean (SD)

Bold text shows p values < 0.05

( ) Number of available information unless from all

Table 2. Socioeconomic factors

	Preeclampsia (n=708)		Healthy controls (n=498)			All controls (n=724)		
	N	% or median (range)	N	% or median (range)	*p* value	N	% or median (range)	*p* value
Education level	(n=698)		(n=496)		0.077	(n=719)		0.154
Basic level [a]	44	6.3	17	3.4		29	4.0	
Upper secondary level [b]	287	41.1	204	41.1		301	41.9	
Tertiary level [c]	367	52.6	275	55.4		389	54.1	
Employment status	(n=659)		(n=468)		**<0.001**	(n=672)		**<0.001**
paid employment	440	66.8	254	54.3		378	56.3	
housewife	144	21.9	173	37.0		237	35.3	
student	38	5.8	28	6.0		42	6.3	
unemployed	37	5.6	13	2.8		15	2.2	
Working hours / week	(n=577)	37.5 (0-73.5)	(n=388)	37.5 (0-60.0)	**0.001**	(n=569)	37.5 (0-90.0)	**0.008**
0	105	18.2	106	27.3		143	25.1	
1 - < 37	97	16.8	65	16.8		100	17.6	
37 - 40	342	59.3	200	51.5		297	52.2	
> 40	33	5.7	17	4.4		29	5.1	
Working hours / week, 0 hours excluded	(n=472)	37.5 (2-73.5)	(n=282)	37.5 (3-60)	0.275	(n=426)	37.5 (2-90)	0.382
Have you been unemployed during the last 12 months?	(n=690)		(n=490)		**0.008**	(n=708)		**0.018**
No	547	79.3	414	84.5		587	82.9	
Yes ≤ 6 months	107	15.5	46	9.4		75	10.6	
Yes ≥ 6 months	36	5.2	30	6.1		46	6.5	
Income level, own estimate	(n=692)		(n=496)		0.729	(n=718)		0.788
Good	309	44.7	210	42.3		309	43.0	
Average	306	44.2	228	46.0		323	45.0	
Poor	77	11.1	58	11.7		86	12.0	
Living area	(n=687)		(n=497)		0.655	(n=719)		0.566
Town with > 20 000 inhabitants	500	72.8	371	74.6		519	72.2	
Town with < 20 000 inhabitants	58	8.4	43	8.7		72	10.0	
Rural	129	18.8	83	16.7		128	17.8	
Marital status	(n=689)		(n=495)		**0.002**	(n=716)		**0.025**
Married	404	58.6	337	68.1		470	65.6	
Cohabitation	264	38.3	151	30.5		229	32.0	
Not cohabiting (with infant's father)	21	3.0	7	1.4		17	2.4	

[a] at most nine years of education

[b] 11 to 12 years of education

[c] 3-6 years of education after upper secondary level, includes polytechnic degrees and lower university degrees, higher university degrees (master's degree) and specialist's degrees in medicine

Bold text shows p values < 0.05

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Table 3. Health and pregnancy information

	Preeclampsia (n=708)		Healthy controls (n=498)			All controls (n=724)		
	N	% or median (range)	N	% or median (range)	p value	N	% or median (range)	*p* value
HEALTH INFORMATION								
Health status, own estimation	(n=694)		(n=493)		**<0.001**	(n=716)		**<0.001**
Good	541	78.0	455	92.3		636	88.8	
Average	133	19.2	34	6.9		67	9.4	
Poor	20	2.9	4	0.8		13	1.8	
Number of sick days during last 12 months [a]	(n=436)	5 (0-75)	(n=248)	5 (0-60)	0.823	(n=370)	5 (0-120)	0.936
< 5	210	48.2	124	50.0		185	50.0	
5-10	152	34.9	93	37.5		134	36.2	
> 10	74	17.0	31	12.5		51	13.8	
Age at menarche (years)	(n=688)	13.0 (9.0-17.0)	(n=490)	13.0 (10.0-18.0)	**0.001**	(n=708)	13.0 (9.0-18.0)	**0.022**
11-15	650	94.5	464	94.7		669	94.5	
< 11	29	4.2	8	1.6		14	2.0	
> 15	9	1.3	18	3.7		25	3.5	
PREGNANCY INFORMATION								
Time to pregnancy (months)	(n=639)	3 (0-144)	(n=461)	2 (0-144)	**0.013**	(n=670)	2 (0-144)	**0.019**
≤ 3	361	56.5	296	64.2		427	63.7	
> 3-12	171	26.8	108	23.4		157	23.4	
> 12	107	16.7	57	12.4		86	12.8	
Morning sickness	610 (n=696)	87.6	454 (n=496)	91.5	**0.033**	649 (n=717)	90.5	0.083
Morning sickness, degree of difficulty, scale 0-100	(n=696)	20 (0-100)	(n=496)	18 (0-100)	0.990	(n=717)	18 (0-100)	0.964
Assisted reproductive technology (ART)	(n=671)		(n=469)		0.157	(n=680)		0.143
Any treatment	84	12.5	46	9.8		68	10.0	
Clomiphene stimulation	27	4.0	20	4.3	0.841	25	3.7	0.740
Insemination	30	4.5	13	2.8	0.138	18	2.6	0.070
Surgical treatment	5	0.7	0	0	0.061	1	0.1	0.098
In vitro fertilization (IVF)	40	6.0	17	3.6	0.075	27	4.0	0.092
Intracytoplasmic sperm injection (ICSI)	10	1.5	6	1.3	0.766	7	1.0	0.447
Other treatment	17	2.5	10	2.1	0.661	15	2.2	0.692

[a] among employed women, does not include absences related to pregnancy
Bold text shows p values < 0.05
( ) Number of available information unless from all

Table 4. Pre-existing medical conditions

	Preeclampsia (n=708)		Healthy controls (n=498)			All controls (n=724)		
	N	%	N	%	*p* value	N	%	*p* value
Any pre-existing medical condition	93 (n=694)	13.4	29 (n=497)	5.8	**<0.001**	66 (n=718)	9.2	**0.012**
Type I diabetes	19 (n=666)	2.9	0 (n=483)	0	**<0.001**	4 (n=691)	0.6	**0.001**
Type II diabetes	5 (n=664)	0.8	0 (n=483)	0	0.056	5 (n=692)	0.7	0.948
Chronic hypertension	55 (n=665)	8.3	0 (n=483)	0	**<0.001**	18 (n=692)	2.6	**<0.001**
Hypercholesterolemia	37 (n=664)	5.6	10 (n=483)	2.1	**0.003**	14 (n=691)	2.0	**0.001**
Allergic rhinitis	159 (n=669)	23.8	127 (n=487)	26.1	0.369	179 (n=697)	25.7	0.412
Asthma	74 (n=664)	11.1	37 (n=480)	7.7	0.053	67 (n=687)	9.8	0.403
Atopic dermatitis	106 (n=662)	16.0	83 (n=484)	17.1	0.609	118 (n=688)	17.2	0.574
Other allergic disease	81 (n=649)	12.5	56 (n=482)	11.6	0.660	93 (n=688)	13.5	0.573
Depression	76 (n=668)	11.4	32 (n=483)	6.6	**0.006**	53 (n=693)	7.6	**0.019**
Panic disorder	24 (n=662)	3.6	17 (n=483)	3.5	0.924	23 (n=692)	3.3	0.762
Other mental disorder	16 (n=662)	2.4	6 (n=482)	1.2	0.154	11 (n=690)	1.6	0.280

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Table 5. Regular/seasonal medication during last 12 months

	Pre-eclampsia (n=708)		Healthy controls (n=498)			All controls (n=724)		
	N	%	N	%	*p* value	N	%	*p* value
Any medication	222	31.4	105	21.1	**<0.001**	201	27.8	0.136
Psychiatric medication	27	3.8	11	2.2	0.116	23	3.2	0.512
Selective serotonin reuptake inhibitors (SSRI)	26	3.7	6	1.2	**0.009**	16	2.2	0.101
Asthma medication	34	4.8	15	3.0	0.121	32	4.4	0.730
Levothyroxine	25	3.5	9	1.8	0.076	22	3.0	0.601
Antihistamine	41	5.8	28	5.6	0.901	45	6.2	0.735
Intranasal steroids	20	2.8	15	3.0	0.849	22	3.0	0.811
IBD [a] or rheumatic disease medication	10	1.4	4	0.8	0.331	8	1.1	0.602
Aspirin	6	0.8	2	0.4	0.348	3	0.4	0.300
Low-molecular-weight heparin	5	0.7	7	1.4	0.228	9	1.2	0.302
Insulin	23	3,2	0	0	**<0.001**	6	0.8	**0.001**
Metformin	6	0.8	0	0	**0.040**	2	0.3	0.147
Proton pump inhibitors	6	0.8	2	0.4	0.348	4	0.6	0.503
Anti hypertensive agents	56	7.9	4	0.8	**<0.001**	26	3.6	**<0.001**
Labetalol	45	6.4	0	0	**<0.001**	16	2.2	**<0.001**
Nifedipine	13	1.8	0	0	**0.002**	2	0.3	**0.004**
ACE inhibitor [b]/ARB [c]	12	1.7	0	0	**0.004**	4	0.6	**0.040**
Other beta blocker	4	0.6	4	0.8	0.616	8	1.1	0.262
Other medication	41	5.8	30	6	0.866	50	6.9	0.387

[a] Inflammatory bowel disease

[b] Angiotensin-converting enzyme inhibitor

[c] Angiotensin II receptor blocker

Bold text shows p values < 0.05

Table 6. Information on study participants' parents.

	Preeclampsia (n=708)		Healthy controls (n=498)			All controls (n=724)		
	N	% or median (range)	N	% or median (range)	p value	N	% or median (range)	p value
Father's education level	(n=677)		(n=486)		**0.012**	(n=703)		**0.033**
Basic level [a]	202	29.8	127	26.1		202	28.7	
Upper secondary level [b]	363	53.6	245	50.4		346	49.2	
Tertiary level [c]	112	16.5	114	23.5		155	22.0	
Mother's education level	(n=684)		(n=491)		0.236	(n=709)		0.412
Basic level [a]	178	26.0	118	24.0		182	25.7	
Upper secondary level [b]	385	56.3	267	54.4		382	53.9	
Tertiary level [c]	121	17.7	106	21.6		145	20.5	
Father's medical conditions								
myocardial infarction	54 (n=659)	8.2	44 (n=472)	9.3	0.506	75 (n=680)	11.0	0.079
stroke	41 (n=664)	6.2	15 (n=476)	3.2	**0.020**	24 (n=684)	3.5	**0.022**
diabetes	81 (n=666)	12.2	58 (n=475)	12.2	0.980	88 (n=683)	12.9	0.689
hypertension	229 (n=663)	34.5	103 (n=470)	21.9	**<0.001**	165 (n=676)	24.4	**<0.001**
mental disorder	36 (n=661)	5.4	22 (n=473)	4.7	0.549	30 (n=679)	4.4	0.385
of which depression	14 (n=661)	2.1	11 (n=473)	2.3	0.814	15 (n=679)	2.2	0.909
Mother's medical conditions								
myocardial infarction	18 (n=686)	2.6	7 (n=484)	1.4	0.170	11 (n=699)	1.6	0.172
stroke	17 (n=686)	2.5	12 (n=484)	2.5	0.999	15 (n=698)	2.1	0.684
diabetes	51 (n=684)	7.5	15 (n=485)	3.1	**0.001**	30 (n=700)	4.3	**0.012**
hypertension	209 (n=678)	30.8	102 (n=483)	21.1	**<0.001**	152 (n=698)	21.8	**<0.001**
mental disorder	49 (n=682)	7.2	18 (n=483)	3.7	**0.013**	27 (n=696)	3.9	**0.007**
of which depression	33 (n=682)	4.8	9 (n=483)	1.9	**0.007**	15 (n=696)	2.2	**0.007**
PE when pregnant with the study participant	69 (n=633)	10.9	13 (n=473)	2.7	**<0.001**	18 (n=678)	2.7	**<0.001**

[a] at most nine years of education

[b] 11 to 12 years of education

[c] 3-6 years of education after upper secondary level, includes polytechnic degrees and lower university degrees, higher university degrees (master's degree) and specialist's degrees in medicine

Bold text shows p values < 0.05

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