Received: 16 November 2021 | Revised: 18 April 2022 | Accepted: 10 May 2022

DOI: 10.1111/aogs.14388

ORIGINAL RESEARCH ARTICLE

Searching for a paternal phenotype for preeclampsia

Noora Jaatinen[1,2] | Tiina Jääskeläinen[3,4] | Eeva Ekholm[1] | Hannele Laivuori[3,5,6,7] | for FINNPEC

[1]Department of Obstetrics and Gynecology, Turku University Central Hospital and University of Turku, Turku, Finland

[2]Department of Obstetrics and Gynecology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

[3]Medical and Clinical Genetics, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

[4]Department of Food and Nutrition, University of Helsinki, Helsinki, Finland

[5]Institute for Molecular Medicine Finland (FIMM), Helsinki Institute of Life Science, University of Helsinki, Helsinki, Finland

[6]Department of Obstetrics and Gynecology, Tampere University Hospital, Tampere, Finland

[7]Center for Child, Adolescent, and Maternal Health Research, Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland

Correspondence
Hannele Laivuori, Faculty of Medicine and Health Technology, Tampere University, Mail Finn-Medi 1, Biokatu 6, 33520 Tampere, Finland.
Email: hannele.laivuori@tuni.fi

Funding information
Jane and Aatos Erkko Foundation; Juho Vainio Foundation; Päivikki and Sakari Sohlberg Foundation; Academy of Finland; Government special state subsidy for the health sciences for the Hospital district of Helsinki and Uusimaa; Research Funds of the University of Helsinki, government special state subsidy for the health sciences for the Hospital District of Helsinki and Uusimaa; Finska Läkaresällskapet; Liv och Hälsa Foundation; Novo Nordisk Foundation; Finnish Foundation for Pediatric Research; Emil Aaltonen Foundation; Sigrid Juselius Foundation; Finnish Foundation for Laboratory Medicine; Seinäjoki Central Hospital; Turku University Foundation

Abstract

Introduction: Preeclampsia (PE) is a heterogeneous disorder and research to date has principally focused on maternal factors. In this study, however, we considered the associations between background factors and preeclampsia in men who fathered preeclamptic and non-preeclamptic pregnancies.

Material and methods: From 2008 to 2011, participants in the Finnish Genetics of Pre-eclampsia Consortium (FINNPEC) cohort completed a questionnaire on their background information. Questionnaire data were available from 586 men who had fathered a preeclamptic pregnancy (PE fathers) and 660 control men who had fathered a non-preeclamptic pregnancy. Two different control groups were established: Group 1: *healthy controls* ($n = 457$), which consisted of fathers whose current partners were healthy women with uncomplicated pregnancies; Group 2: *other controls* ($n = 203$), which also included fathers whose current partners had other pregnancy complications.

Results: The PE fathers more often reported preeclampsia in a previously fathered pregnancy ($p < 0.05$ for all). The PE and control fathers were similar in age, body mass index, smoking, and preexisting medical conditions. There were no differences in the socioeconomic background or health history of the PE and control fathers or their parents.

Conclusions: In the FINNPEC study cohort, the occurrence of preeclampsia in a previously fathered pregnancy was more common among the men who had fathered a preeclamptic pregnancy; other paternal phenotypic and lifestyle characteristics did not play a significant role in preeclampsia susceptibility of their partners.

Abbreviations: BMI, body mass index; CI, confidence interval; FINNPEC, Finnish Genetics of Pre-eclampsia Consortium; OR, odds ratio; PE, preeclampsia.

Noora Jaatinen and Tiina Jääskeläinen contributed equally.

KEYWORDS
lifestyle, paternal, phenotype, preeclampsia, pregnancy, pregnancy complication, risk factor

1 | INTRODUCTION

Preeclampsia (PE) is a complex vascular disorder in pregnancy characterized by new-onset hypertension and proteinuria after 20 weeks of gestation or new-onset PE-associated signs in the absence of proteinuria.[1] The etiology of PE is still unknown, making strategies for its prevention challenging. A wide range of maternal risk factors have been recognized, including nulliparity, multifetal gestation, previous history of PE, chronic hypertension, obesity, diabetes mellitus, age >35 years at first pregnancy and smoking.[2] While PE is generally considered a maternal disease, it can also be seen as a maternal and paternal disease with both fetal and maternal manifestations.[3] In addition, the placenta is the cornerstone of the pathophysiology of PE, and it includes important paternal genetic determinants.[4]

In 1981, Astin et al. published a study suggesting a possible role of paternal immunogenetic factors in the pathogenesis of PE. They presented two women who had severe PE and had become pregnant with the same man.[5] The role of the father in the onset of PE has also been demonstrated in a few large population studies. For example, men born from a preeclamptic pregnancy have been shown to be twice as likely to father one.[6] In addition, men who have already fathered a preeclamptic pregnancy have been shown to be nearly twice as likely to father another one with a different partner, regardless of the mother's pregnancy history.[7]

Preconceptional paternal health factors as defined by a number of metabolic syndrome components and chronic diseases have been independently associated with increased odds of PE in healthy partners.[8] Regarding phenotype, paternal obesity has been shown to be an independent risk factor for small-for-gestational-age infants independently of maternal factors.[9] However, it is still unclear whether paternal obesity affects the risk of PE. Myklestad et al. found that men who fathered a pregnancy with PE or gestational hypertension had a greater body mass index (BMI) than men who fathered pregnancies without these complications.[10] Furthermore, Rigó et al. showed that an increase in the risk of PE was seen in pregnancies fathered by men with a familial history of early-onset cardiovascular disease and/or hypertension.[11]

Our aim in the current study was to study whether paternal phenotype is associated with a risk of PE in the Finnish Genetics of Preeclampsia Consortium (FINNPEC) cohort.

Key message

In the FINNPEC study cohort, the phenotype and lifestyle of the fathers did not play a significant role in preeclampsia susceptibility of their partners.

2 | MATERIAL AND METHODS

2.1 | Study design

The data for the present study came from the prospective arm of the FINNPEC cohort. The FINNPEC is a cross-sectional case–control multicenter study using a nationwide clinical and DNA database of women with and without PE that included their partners and infants. The study was established to identify genetic risk factors for PE. The details of the study design, methods and procedures have been previously published.[12]

2.2 | Study Review use of the term "subjects"

A total of 719 men who had fathered a preeclamptic pregnancy (PE fathers) and 899 control men who had fathered a non-preeclamptic pregnancy were recruited for the study between 2008 and 2011. Men who had a minimum age of 18 years and provided informed consent based on information in either Finnish or Swedish were eligible for this study. The inclusion criteria for the index mothers were a minimum age of 18 years, a singleton pregnancy, and the ability to provide informed consent. PE was defined as hypertension and proteinuria occurring after 20 weeks of gestation as based on the American College of Obstetricians and Gynecologists' 2002 criteria.[13] Hypertension was defined as systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg. Proteinuria was defined as the urinary excretion of ≥0.3 g protein in a 24-h specimen, 0.3 g/L, or two ≥1+ readings on a dipstick in a random urine sample with no evidence of a urinary tract infection. Each diagnosis was independently verified from medical records by a research nurse and research physician.

The participating fathers filled in a detailed questionnaire on their background information (Appendix S1), including data on their reproductive history, personal and family medical history, and socioeconomic and lifestyle factors. Information on previously fathered children and PE in these prior pregnancies was obtained from the background information questionnaires completed by the fathers and index mothers. The ages of the fathers were obtained from the written consent and ethnicities from the hospital records. Each father filled in the questionnaire during the index mother's pregnancy or shortly after delivery. Information on index mothers' age, pre-pregnancy weight and height and parity were obtained from the hospital records and maternity cards. Data on index mothers' smoking were collected from the maternity cards and complemented from the background information questionnaires.

In July 2019, questionnaires on background information were available from 586 PE fathers and 660 control fathers. Two different control groups were established for the current study: one a group of healthy controls (n = 457) that consisted of fathers whose current partners were healthy women with uncomplicated pregnancies and another for other controls (n = 203) that included fathers whose current partners had pregnancy complications (gestational diabetes, gestational hypertension, proteinuria without high blood pressure, placental insufficiency, fetal death, and small-for-gestational-age infants [data for partners' pregnancy complications is not shown]) other than PE.

2.3 | Statistical analyses

Statistical tests were performed using SPSS STATISTICS 25.0 (IBM Corp.). Background information on the PE fathers and the two different control groups were compared separately (PE vs healthy controls and PE vs other controls). The normality of the variable distributions was verified graphically and with a Kolmogorov–Smirnov test. Differences between the groups were tested with logistic regression analysis with odds ratios (OR) and 95% confidence intervals (CI) or with Fisher's exact test. Multivariable-adjusted logistic regression analyses were conducted to examine which paternal risk factors were independently associated with PE after controlling for known maternal risk factors for PE (index mother's BMI, age at birth, parity and smoking during pregnancy). p-values of <0.05 were considered statistically significant.

2.4 | Ethical approval

All participants provided written informed consent, and the FINNPEC study protocol was approved by the coordinating Ethics Committee of the Hospital District of Helsinki and Uusimaa (149/EO/2007) on October 7, 2007 (updated May 16, 2018). All data used in this manuscript are covered by the original approval of the coordinating Ethics Committee of the Hospital District of Helsinki and Uusimaa. Moreover, the original approval was updated regularly during the course of the project.

3 | RESULTS

3.1 | Basic characteristics of the study population

The basic characteristics of the participating fathers are presented in Table 1. The fathers in the control groups had previously fathered more children in total but there was no difference after adjusting for maternal risk factors. PE fathers more often reported PE in a previously fathered pregnancy. Almost all of these previous cases of PE were with the index mother. The groups were similar regarding age, BMI and smoking.

3.2 | Health history and socioeconomic factors

This study did not show differences in the health history (Table 2, Table S1a,b) or socioeconomic background (Table S2a,b) of the PE fathers as compared with the controls.

3.3 | Parents of study participants

The educational and medical history of the parents of the FINNPEC fathers is presented in Table S3a,b. The parents of the PE fathers did not suffer from more medical conditions than the parents of the controls. Mental disorders including depression were more prevalent in the fathers of the healthy control group fathers. No differences were detected between the groups regarding parental education.

4 | DISCUSSION

PE is a heterogeneous disorder, and research to date has principally focused on maternal factors. In the current study, we extensively evaluated the background and health information of the men in the FINNPEC study cohort who fathered both preeclamptic and non-preeclamptic pregnancies. The occurrence of PE in a previously fathered pregnancy was more common among the men who had fathered a preeclamptic pregnancy. The PE and control fathers were similar in age, BMI, smoking and preexisting medical conditions. There were no differences in socioeconomic background or health history of the FINNPEC fathers or their parents.

In mothers, multiparity has been shown to protect against PE if the previous pregnancy was not complicated by PE.[14] Furthermore, primipaternity has been reported as an independent risk factor for PE in multigravidae,[15,16] possibly due to immune maladaptation on the feto-maternal interface.[16] In our study the number of first-time fathers did not differ between the groups after adjusting for index mother's BMI, age at birth, parity and smoking during pregnancy. However, the PE fathers more often reported PE in a previously fathered pregnancy with the index mother.

We did not observe any association between paternal BMI and PE. Previously, paternal obesity has been reported to be associated with the risk of PE.[10] In an extensive study by Myklestad et al. comprised of more than 14 000 families, the data on weight and height were obtained through physical examinations.[10] In contrast, our data on paternal BMI were based on self-reported height and weight at recruitment, and this may have thus contributed to our result.

Paternal age has been suggested as a risk factor for fathering a preeclamptic pregnancy in a study that surveyed 81 213 deliveries from 1965–1976 in Jerusalem,[17] but more recently, larger studies from the USA have found no association between PE and paternal age.[18,19] Hurley et al. examined more than 1 million births in the state of Ohio from 2006 to 2012 and Khadwala et al. examined more than 40 million births in the USA from 2007 to 2016; they identified no associations between paternal age and PE.[18,19] In line with these US studies, we did not observe any association between paternal age and PE.

TABLE 1 Basic characteristics of the FINNPEC fathers

	Preeclampsia (n = 586)		Healthy controls (n = 457)							
	n	% or median (range) or mean (SD)	n	% or median (range) or mean (SD)	OR	95% CI	p-value	OR adj[a]	95% CI adj[a]	p-value adj[a]
Age at enrollment, years		31.8 (6.2)[b]		31.5 (5.8)	1.01	0.99–1.03	0.522	0.99	0.953–1.03	0.589
Ethnicity: Caucasian (ref. = other)	577	98.5	449	98.2	1.14	0.44–2.98	0.786	1.21	0.43–3.47	0.718
Any children fathered before index pregnancy	171	30.3	215	49.3	0.45	0.35–0.58	**<0.001**	0.84	0.50–1.40	0.497
Previous children fathered with index mother[b]	129 (n = 170)	75.9	196 (n = 214)	91.6	0.29	0.16–0.53	**<0.001**	1.06	0.29–3.86	0.934
Previous children fathered with different mother than index mother[b]	50 (n = 164)	30.5	31 (n = 209)	14.8	2.52	1.52–4.18	**<0.001**	0.82	0.35–1.94	0.654
PE in previously fathered pregnancy with index mother[b]	55 (n = 170)	32.4	3 (n = 215)	1.4	33.80	10.34–110.43	**<0.001**	42.33	12.49–143.41	**<0.001**
PE in previously fathered pregnancy with different mother than index mother[b]	1 (n = 170)	0.6	0 (n = 215)	0			0.442[c]			
BMI[d], kg/m^2		25.7 (14.8–46.9)		25.4 (18.6–39.7)	1.03	0.99–1.06	0.161	0.98	0.95–1.02	0.405
Smoking before index mother's pregnancy	203	35.1	161	35.9	0.97	0.75–1.25	0.791	1.13	0.84–1.52	0.409
Smoking during index mother's pregnancy	186	32.0	145	32.1	1.00	0.77–1.30	0.982	1.10	0.82–1.48	0.533
	Preeclampsia (n = 586)		**Other controls (n = 203)**							
	n	**% or median (range) or mean (SD)**	**n**	**% or median (range) or mean (SD)**	**OR**	**95% CI**	***P*-value**	**OR adj[a]**	**95% CI adj[a]**	***P*-value adj[a]**
Age at enrollment, years		31.8 (6.2)[b]		32.3 (5.5)	0.99	0.96–1.01	0.297	0.99	0.95–1.04	0.708
Ethnicity: Caucasian (ref. = other)	577	98.5	200	99.5	0.32	0.04–2.55	0.282	0.38	0.05–3.04	0.360

(Continues)

TABLE 1 (Continued)

	Preeclampsia ($n = 586$)		Other controls ($n = 203$)							
	n	% or median (range) or mean (SD)	*n*	% or median (range) or mean (SD)	OR	95% CI	*P*-value	OR adj[a]	95% CI adj[a]	*P*-value adj[a]
Any children fathered before index pregnancy	171	30.3	81	42.0	0.60	0.43–0.84	**0.003**	1.07	0.59–1.92	0.831
Previous children fathered with index mother[b]	129 ($n = 170$)	75.9	69 ($n = 81$)	85.2	0.55	0.27–1.11	0.094	1.14	0.29–4.58	0.852
Previous children fathered with different mother than index mother[b]	50 ($n = 164$)	30.5	15 ($n = 80$)	18.8	1.90	0.99–3.65	0.054	1.16	0.40–3.38	0.786
PE in previously fathered pregnancy with index mother[b]	55 ($n = 170$)	32.4	8 ($n = 81$)	9.9	4.36	1.97–9.69	**<0.001**	6.86	2.75–17.13	**<0.001**
PE in previously fathered pregnancy with mother different than index mother[b]	1 ($n = 170$)	0.6	1 ($n = 81$)	1.2			0.542[c]			
BMI[d], kg/m^2		25.7 (14.8–46.9)		25.9 (14.8–46.9)	0.98	0.94–1.03	0.447	0.98	0.93–1.02	0.341
Smoking before index mother's pregnancy	203	35.1	81	40.1	0.81	0.58–1.12	0.200	0.83	0.58–1.19	0.310
Smoking during index mother's pregnancy	186	32.0	71	35.7	0.85	0.61–1.19	0.343	0.85	0.59–1.23	0.389

Note: Differences between PE and control fathers were determined using logistic regression analysis with odds ratios (OR) and 95% confidence intervals (CI). No mathematical correction was made for multiple comparisons. Bold text shows *P*-values <0.05. () Number of unknown data were shown if number of unknown data was over 10%.

PE, preeclampsia.

[a]Logistic regression adjusted for index mother's BMI, age at birth, parity and smoking during pregnancy.

[b]Of those who had had children before.

[c]Fisher's exact test.

[d]Body mass index.

TABLE 2 Information on health and own birth of the FINNPEC fathers

	Preeclampsia ($n = 586$)		Healthy controls ($n = 457$)							
	n	% or median (range)	*n*	% or median (range)	OR	95% CI	*p*-value	OR adj[a]	95% CI adj[a]	*p*-value adj[a]
Health										
Health status, own estimation	($n = 583$)		($n = 455$)							
Good (ref.)	502	86.1	407	89.5						
Average	75	12.9	45	9.9	1.35	0.91–2.00	0.132	1.19	0.77–1.83	0.438
Poor	6	1.0	3	0.7	1.62	0.40–6.52	0.496	1.00	0.23–4.30	0.999
Number of sick days during last 12 months[b]	($n = 512$)		($n = 405$)							
<5 (ref.)	312	60.9	254	62.7						
5–10	139	27.1	110	27.2	1.03	0.76–1.39	0.853	1.09	0.78–1.51	0.624
>10	61	11.9	41	10.1	1.21	0.79–1.86	0.381	1.15	0.72–1.84	0.550
Own birth										
Own birthweight (kg)	($n = 509$)	3.600 (1.280–5.300)	($n = 370$)	3.545 (1.900–5.050)	0.99	0.78–1.25	0.906	1.05	0.82–1.35	0.717
Own gestational age at birth (weeks)	($n = 464$)	40 (24–43)	($n = 320$)	40 (29–43)						
≥41 0/7 (ref.)	75	16.2	73	22.8						
37 0/7–40 6/7	355	76.5	230	71.9	1.50	1.05–2.16	**0.028**	1.60	1.08–2.37	**0.019**
<37 0/7	34	7.3	17	5.3	1.95	1.00–3.79	**0.050**	1.62	0.79–3.30	0.187
Born from a PE pregnancy	($n = 570$)		($n = 447$)							
Yes	15	2.6	12	2.7	0.98	0.45–2.12	0.981	0.71	0.31–1.65	0.429
No (ref.)	456	80.0	358	80.1						
I do not know	99	17.4	77	17.2	1.01	0.73–1.40	0.955	0.96	0.67–1.36	0.797
	Preeclampsia ($n = 586$)		**Other controls ($n = 203$)**							
	n	% or median (range)	*n*	% or median (range)	OR	95% CI	*p*-value	OR adj[a]	95% CI adj[a]	*p*-value adj[a]
HEALTH										
Health status, own estimation	($n = 583$)		($n = 202$)							
Good (ref.)	502	86.1	178	88.1						
Average	75	12.9	23	11.4	1.16	0.70–1.90	0.567	1.21	0.72–2.05	0.469

(Continues)

TABLE 2 (Continued)

	Preeclampsia (n = 586)		Other controls (n = 203)							
	n	% or median (range)	n	% or median (range)	OR	95% CI	p-value	OR adj[a]	95% CI adj[a]	p-value adj[a]
Poor	6	1.0	1	0.5	2.13	0.25–17.79	0.486	2.17	0.25–18.6	0.479
Number of sick days during last 12 months[b]	(n = 512)		(n = 181)							
<5 (ref.)	312	60.9	105	58.0						
5–10	139	27.1	49	27.1	0.96	0.64–1.42	0.817	1.03	0.69–1.54	0.900
>10	61	11.9	27	14.9	0.76	0.46–1.26	0.760	0.88	0.51–1.51	0.648
Own birth										
Own birthweight (kg)	(n = 509)	3.60 (1.28–5.30)	(n = 176)	3.61 (1.60–5.35)	0.82	0.61–1.14	0.193	0.81	0.59–1.09	0.162
Own gestational age at birth (weeks)	(n = 464)	40 (24–43)	(n = 160)	40 (32–43)						
≥41 0/7 (ref.)	75	16.2	36	22.5						
37 0/7–40 6/7	355	76.5	116	72.5	1.47	0.94–2.30	0.093	1.48	0.94–2.35	0.094
<37 0/7	34	7.3	8	5.0	2.04	0.86–4.85	0.107	2.22	0.89–5.56	0.088
Born from a PE pregnancy	(n = 570)		(n = 200)							
Yes	15	2.6	10	5.0	0.50	0.22–1.14	0.098	0.45	0.20–1.06	0.066
No (ref.)	456	80.0	152	76.0						
I do not know	99	17.4	38	19.0	0.87	0.57–1.32	0.507	1.01	0.65–1.57	0.981

Note: Differences between PE and control fathers were determined using logistic regression analysis with odds ratios (OR) and 95% confidence intervals (CI). No mathematical correction was made for multiple comparisons. Bold text shows p-values <0.05. () Number of available information unless from all.

Abbreviation: PE, preeclampsia.

[a]Logistic regression adjusted for index mother's BMI, age at birth, parity and smoking during pregnancy.

[b]Among employed fathers.

To our knowledge, the role of paternal smoking/maternal passive smoking has only been previously investigated in a prospective Norwegian Mother and Child cohort.[20] In that study, passive smoke exposure alone was not associated with reduced odds of PE. This is in line with our finding that smoking status did not differ between the PE and control fathers.

To our knowledge, there have been no previous studies that considered paternal socioeconomic status and the risk of PE. Socioeconomic status as estimated by education and income was similar in the PE and control fathers. Likewise, we found no association between PE and socioeconomic status in an earlier study on FINNPEC women.[21] In contrast, many studies have reported an association between low maternal socioeconomic status and PE.[22,23] The lack of association in our cohort may be influenced by the free prenatal care, free university level education, and the rather small differences between social classes in Finland.[21] This same explanation may apply to paternal socioeconomic status and PE.

The groups of fathers reported comparably often having been born from PE and normal pregnancies, which is in contrast to some previous studies.[6,24] Men who themselves were born in a PE pregnancy have been shown to have an increased risk of PE in the pregnancies that they subsequently father.[6] These findings suggest a role of paternal genes in the increased risk of PE through the fetal genome. Unfortunately, in the present study, a large number of the fathers did not know whether their mother had PE. It would be of interest to replicate our analyses by utilizing registry-based data, in line with some previous studies. A larger study population would have allowed us to compare the incidence of PE in previously fathered pregnancies with a different partner than the index mother.

PE is known to affect the long-term health of the mother and child. In particular, a well-established association exists between PE and an increased risk of later-life cardiovascular disease.[25] However, there are very little long-term data on the morbidity and mortality of the fathers. The current study found no differences in the preexisting medical conditions between the PE and control fathers. One of the strengths of the present study is that the data on education and medical history extend to the parents of the pregnant mother and the father. This study found no significant differences in the socioeconomic background or health history in the parents of the FINNPEC fathers.

Self-reported information gained through questionnaires is prone to recall bias which can be considered as a limitation of this study. It is likely that the fathers were not aware of all details of the obstetric history concerning their partners' pregnancies. Further, the accuracy of information pertaining to the fathers' parents' health and reproductive history might vary from case to case. Multiple hypothesis testing can be considered a weakness in this study. The *p*-values reported in the tables have not been Bonferroni-corrected. We do note that none of our tests would be significant at the 0.05 level after a correction for multiple testing is applied. However, overadjustment for multiple comparisons may increase type II error, which reduces the power to detect significant differences.

The clustering of PE cases within families has been recognized since the 20th century as suggesting a genetic component to this disorder.[26,27] Deciphering the genetic background of PE is challenging, not least of all because the phenotype is expressed only in pregnancy.[28] It has been suggested that paternal genes contribute to the risk of maternal hypertensive disorders in pregnancy (PE and gestational hypertension) mediated by the fetal genes involved in placentation.[29] However, this rather new approach for evaluating of the role of the paternal-fetal genotype on the susceptibility for PE has led to inconsistent and conflicting results among the few studies conducted so far.[30] In the current FINNPEC study, analyses on the paternal genotypes are ongoing.

5 | CONCLUSION

Our study has provided information on the role of paternal factors in PE pregnancies in the FINNPEC study cohort. Our study suggests that the phenotype and lifestyle of the fathers did not play a significant role in PE susceptibility of their partners. Studies addressing genetic and epigenetic mechanisms are needed to improve our understanding of the role of the father in the risk of PE.

AUTHOR CONTRIBUTIONS

NJ, TJ, EE and HL designed the research. The FINNPEC core investigator group established the study cohort. NJ analyzed the data. NJ and TJ wrote the first draft of the manuscript. TJ, EE and HL and contributed to the data analysis and interpretation and revised the manuscript. All authors read and approved the final manuscript.

ACKNOWLEDGMENTS

We appreciate the expert technical assistance of Eija Kortelainen and the contributions of the members and assisting personnel of the FINNPEC Study Group. We would also like to acknowledge biostatistician Paula Bergman for help analyzing the data.

The Finnish Genetics of Pre-eclampsia Consortium (FINNPEC) core investigator group. *Hannele Laivuori*: principal investigator; Medical and Clinical Genetics, University of Helsinki and Helsinki University Hospital, Helsinki, Finland; Institute for Molecular Medicine Finland, Helsinki Institute of Life Science, University of Helsinki, Helsinki, Finland; Department of Obstetrics and Gynecology, Tampere University Hospital and Tampere University, Faculty of Medicine and Health Technology, Center for Child, Adolescent and Maternal Health, Tampere, Finland. *Seppo Heinonen*: Obstetrics and Gynecology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland. *Eero Kajantie*: PEDEGO Research Unit, Medical Research Center Oulu, Oulu University Hospital and University of Oulu, Oulu, Finland; Public Health Promotion Unit, National Institute for Health and Welfare, Helsinki and Oulu, Finland; Children's Hospital, University of Helsinki and Helsinki University Hospital, Helsinki, Finland; Department of Clinical and Molecular Medicine, Norwegian University of Health and Technology, Trondheim, Norway. *Juha Kere*: Department of Biosciences and Nutrition, Karolinska Institutet, Huddinge, Sweden; Folkhälsan Research Center and Stem Cells and Metabolism Research Program, University of Helsinki, Helsinki, Finland. *Katja Kivinen*: Institute for Molecular Medicine Finland, Helsinki Institute of Life Science, University

of Helsinki, Helsinki, Finland. *Anneli Pouta*: Department of Government Services, National Institute for Health and Welfare, Helsinki, Finland.

CONFLICT OF INTEREST

None.

FUNDING INFORMATION

The FINNPEC study was supported by the Jane and Aatos Erkko Foundation, Juho Vainio Foundation, Päivikki and Sakari Sohlberg Foundation, Academy of Finland, Research Funds of the University of Helsinki, government special state subsidy for the health sciences for the Hospital District of Helsinki and Uusimaa, Finska Läkaresällskapet, Liv och Hälsa Foundation, Novo Nordisk Foundation, Finnish Foundation for Pediatric Research, Emil Aaltonen Foundation, Sigrid Juselius Foundation, and Finnish Foundation for Laboratory Medicine. NJ was supported by state research financing for a local hospital (Seinäjoki Central Hospital) and the Turku University Foundation.

ORCID

Noora Jaatinen https://orcid.org/0000-0002-8484-0976
Hannele Laivuori https://orcid.org/0000-0003-3212-7826

REFERENCES

1. Gestational hypertension and preeclampsia. ACOG practice bulletin, number 222. American College of Obstetricians and Gynecologists. *Obstet Gynecol*. 2020;135:e237-e260.
2. Eiland E, Nzerue C, Faulkner M. Preeclampsia 2012. *J Pregnancy*. 2012;2012:1-7.
3. Dekker GA, Robillard PY. Preeclampsia: a Couple's disease with maternal and fetal manifestations. *Curr Pharm Des*. 2005;11:699-710.
4. Galaviz-Hernandez C, Sosa-Macias M, Teran E, Garcia-Ortiz JE, Lazalde-Ramos BP. Paternal determinants in preeclampsia. *Front Physiol*. 2018;9:1870.
5. Astin M, Scott JR, Worley RJ. Pre-eclampsia/eclampsia: a fatal father factor. *Lancet*. 1981;318:533.
6. Esplin MS, Fausett MB, Fraser A, et al. Paternal and maternal components of the predisposition to preeclampsia. *N Engl J Med*. 2001;344:867-872.
7. Lie RT, Rasmussen S, Brunborg H, Gjessing HK, Lie-Nielsen E, Irgens LM. Fetal and maternal contributions to risk of pre-eclampsia: population based study. *BMJ*. 1998;316:1347.
8. Murugappan G, Li S, Leonard SA, Winn VD, Druzin ML, Eisenberg ML. Association of preconception paternal health and adverse maternal outcomes among healthy mothers. *Am J Obstet Gynecol MFM*. 2021;3:100384.
9. McCowan LM, North RA, Kho EM, et al. Paternal contribution to small for gestational age babies: a multicenter prospective study. *Obesity*. 2011;19:1035-1039.
10. Myklestad K, Vatten LJ, Salvesen KÅ, Davey Smith G, Romundstad PR. Hypertensive disorders in pregnancy and paternal cardiovascular risk: a population-based study. *Ann Epidemiol*. 2011;21:407-412.
11. Rigó J, Boze T, Derzsy Z, et al. Family history of early-onset cardiovascular disorders is associated with a higher risk of severe pre-eclampsia. *Eur J Obstet Gynecol Reprod Biol*. 2006;128:148-151.
12. Jääskeläinen T, Heinonen S, Kajantie E, et al. Cohort profile: the Finnish genetics of pre-eclampsia consortium (FINNPEC). *BMJ Open*. 2016;6:e013148.
13. ACOG Committee on Practice Bulletins—Obstetrics. ACOG practice bulletin. Diagnosis and management of preeclampsia and eclampsia. Number 33, January 2002. *Obstet Gynecol*. 2002;99:159-167.
14. Luo Z-C, An N, Xu H-R, Larante A, Audibert F, Fraser WD. The effects and mechanisms of primiparity on the risk of pre-eclampsia: a systematic review. *Paediatr Perinat Epidemiol*. 2007;21:36-45.
15. Hercus A, Dekker G, Leemaqz S. Primipaternity and birth interval; independent risk factors for preeclampsia. *J Matern Neonatal Med*. 2018;33:303-306.
16. Tubbergen P, Lachmeijer AMA, Althuisius SM, Vlak MEJ, Van Geijn HP, Dekker GA. Change in paternity: a risk factor for preeclampsia in multiparous women? *J Reprod Immunol*. 1999;45:81-88.
17. Harlap S, Paltiel O, Deutsch L, et al. Paternal age and preeclampsia. *Epidemiology*. 2002;13:660-667.
18. Hurley EG, DeFranco EA. Influence of paternal age on perinatal outcomes. *Am J Obstet Gynecol*. 2017;217(566):e1-e6.
19. Khandwala YS, Baker VL, Shaw GM, Stevenson DK, Lu Y, Eisenberg ML. Association of paternal age with perinatal outcomes between 2007 and 2016 in the United States: population based cohort study. *BMJ*. 2018;363:k4372.
20. Engel SM, Scher E, Wallenstein S, et al. Maternal active and passive smoking and hypertensive disorders of pregnancy: risk with trimester-specific exposures. *Epidemiology*. 2013;24:379-386.
21. Jaatinen N, Jääskeläinen T, Laivuori H, Ekholm E. The non-traditional and familial risk factors for preeclampsia in the FINNPEC cohort. *Pregnancy Hypertens*. 2021;23:48-55.
22. Silva LM, Coolman M, Steegers EAP, et al. Low socioeconomic status is a risk factor for preeclampsia: the generation R study. *J Hypertens*. 2008;26:1200-1208.
23. Bilano VL, Ota E, Ganchimeg T, Mori R, Souza JP. Risk factors of pre-eclampsia/eclampsia and its adverse outcomes in low- and middle-income countries: a WHO secondary analysis. *PLoS One*. 2014;9:e91198.
24. Skjærven R, Vatten LJ, Wilcox AJ, Rønning T, Irgens LM, Lie RT. Recurrence of pre-eclampsia across generations: exploring fetal and maternal genetic components in a population based cohort. *BMJ*. 2005;331:877.
25. Brown MC, Best KE, Pearce MS, Waugh J, Robson SC, Bell R. Cardiovascular disease risk in women with pre-eclampsia: systematic review and meta-analysis. *Eur J Epidemiol*. 2013;28:1-19.
26. Chesley LC, Annitto JE, Cosgrove RA. The familial factor in toxemia of pregnancy. *Obstet Gynecol*. 1968;32:303-311.
27. Arngrimsson R, Björnsson S, Geirsson RT, Björnsson H, Walker JJ, Snaedal G. Genetic and familial predisposition to eclampsia and pre-eclampsia in a defined population. *BJOG An Int J Obstet Gynaecol*. 1990;97:762-769.
28. Williams PJ, Pipkin FB. The genetics of pre-eclampsia and other hypertensive disorders of pregnancy. *Best Pract Res Clin Obstet Gynaecol*. 2011;25:405-417.
29. Cross J. The genetics of pre-eclampsia: a feto-placental or maternal problem? *Clin Genet*. 2003;64:96-103.
30. Zusterzeel PLM, Te Morsche R, Raijmakers MTM, Roes EM, Peters WHM, Steegers EAP. Paternal contribution to the risk for pre-eclampsia. *J Med Genet*. 2002;39:44-45.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Jaatinen N, Jääskeläinen T, Ekholm E, Laivuori H, for FINNPEC. Searching for a paternal phenotype for preeclampsia. *Acta Obstet Gynecol Scand*. 2022;101:862-870. doi: 10.1111/aogs.14388