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Chronic hypertension in women after perinatal exposure to preeclampsia, being born small for gestational age or preterm

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Running head: Hypertension after perinatal exposure

ABSTRACT

Background: There is an established association between adverse events during perinatal life and chronic hypertension in adult life. However, disadvantageous conditions often coexist in the same pregnancy. We investigated single and joint perinatal exposure to preeclampsia, being born small for gestational age (SGA) or preterm and subsequent risk of chronic hypertension.

Methods: The study population consisted of 731,008 primiparous women from Norway and Sweden registered in the Medical Birth Registers, both as infants and as first time mothers between 1967-2009 (Norway) and 1973-2010 (Sweden). Risk of chronic hypertension in early pregnancy was calculated in women perinatally exposed to preeclampsia, born SGA or preterm by log-binominal regression analysis, and adjusted for maternal age and level of education in the 1st generation.

Results: The rate of chronic hypertension was 0.4%. Risk of chronic hypertension was associated with single perinatal exposure to preeclampsia, being born SGA or preterm with adjusted relative risks (95% confidence intervals, CI) 2.2 (95% CI 1.8, 2.7), 1.1 (95% CI 1.0, 1.3) and 1.3 (95% CI 1.0, 1.5) respectively. The risks increased after joint exposures, with an almost 4-fold risk increase after perinatal exposure to preeclampsia and preterm birth. Additional adjustment for BMI and smoking in the 2nd generation in a subset of the cohort only had a minor impact on the results.

Conclusions: Perinatal exposure to preeclampsia, being born SGA or preterm is independently associated with increased risk of chronic hypertension. The highest risk was seen after exposure to preeclampsia, especially if combined with SGA or preterm birth.

Key words: chronic hypertension; preeclampsia; small for gestational age; preterm birth

INTRODUCTION

Hypertension is one of the most important risk factors for cardiovascular disease, affecting one billion people worldwide, and is implicated in over nine million deaths every year.¹ There is a heritability of hypertension, considered to be in the range of 30% to 60%, with multiple contributory genes.² Women with pregnancies complicated by preeclampsia, intrauterine growth restriction (IUGR) and preterm birth have higher risks of cardiovascular disease later in life,³ with a 4 to 5-fold increased risk of chronic hypertension after a pregnancy complicated by preeclampsia.⁴ These risks may be higher when women have several of these complications.⁵ Furthermore, perinatal exposure to preeclampsia, IUGR and preterm birth is associated with chronic diseases later in life, among them chronic hypertension.⁶⁻⁸ Preeclampsia, IUGR and preterm birth are all complications of pregnancy associated with inadequate placentation, and they often occur together.⁹

Studies have shown an inverse association between size at birth and blood pressure in childhood¹⁰ and in adulthood.^{11, 12} However, findings on the effects of perinatal exposure to preeclampsia, IUGR and preterm birth on adult blood pressure are contradictory, and only a few studies have taken into account that exposures are often concurrent in the same pregnancy.^{13, 14} We are not aware of any previous studies that have analysed the separate and joint effects of perinatal exposure to preeclampsia, IUGR or preterm birth on the risk of chronic hypertension in adult life.

The aim of the study was to investigate the subsequent risk of chronic hypertension after single and joint perinatal exposure to preeclampsia, being born small for gestational age

(SGA) or preterm in a cohort of women expecting their first child. We also investigated if there was interaction between the exposures.

METHODS

Data sources

The Medical Birth Registry of Norway (MBRN) contains data on all births in Norway from 16 completed gestational weeks since 1967, whereas the Swedish Medical Birth Register (MBR) was founded in 1973 and contains information on births in Sweden from 22 completed gestational weeks. Both registers are based on mandatory notifications and contain prospectively collected data on maternal characteristics and medical history, pregnancy complications, labour and delivery, as well as characteristics and medical conditions of the infant. The woman's medical and obstetric history and family situation is registered in early pregnancy. Diseases and complications during pregnancy and delivery are recorded by the midwife and/or doctor responsible for delivery. Information is registered in the birth registers using the International Classification of Diseases (ICD). In Norway and Sweden, all legal residents are assigned a unique personal identity number at birth or immigration. The personal identity number allows an individual's record to be linked between registers. The study was approved by the regional ethical review board of the Karolinska Institutet. The study was also approved by the internal review board of the Medical Birth Registry of Norway and by the regional ethics committee, REK Vest, Norway.

Study population

The study population consisted of all mother-daughter pairs registered in the birth registers of Norway and Sweden, where the woman of 1st generation gave birth in Norway from 1967

(n=718,744), or in Sweden from 1973 (n=731,903), and the woman of 2nd generation gave birth in Norway in 2009 or earlier, or in Sweden in 2010 or earlier (Figure 1). In order to investigate each individual only once, we excluded all women from the 2nd generation who were not primiparous. Multiple pregnancies and pregnancies complicated by pre-gestational diabetes or chronic hypertension were excluded from the 1st generation in order to remove other perinatal exposures with possible cardiovascular effects. Likewise, pregnancies exposed to pre-gestational diabetes in the 2nd generation were also excluded as diabetes is a known risk factor for cardiovascular disease.¹⁵ The final cohort included 731,008 women (Figure 1).

Perinatal exposure

The perinatal exposures that we examined included women being born after a pregnancy complicated by preeclampsia, being born small for gestational age (SGA) and being delivered preterm. Preeclampsia was clinically defined as de novo blood pressure $\geq 140/90$ mmHg in combination with proteinuria (≥ 0.3 g/24 hours) or oedema after gestational week 20 until the middle of the 1980s; thereafter, proteinuria was compulsory. Preeclampsia was identified by the ICD-codes (Supplemental table 1). SGA was defined as birth weight $< 10^{\text{th}}$ percentile of expected birth weight for gestational age according to the Swedish reference curve for foetal growth.¹⁶ SGA was further classified as severe SGA ($< 3^{\text{rd}}$ percentile) and moderate SGA (3^{rd} to $< 10^{\text{th}}$ percentile). Most pregnancies in the cohort were dated by last menstrual period, as early second trimester ultrasound scan for estimation of gestational age was introduced during the end of the 80s in both countries. We considered birth weights ≥ 5 standard deviations above or under the expected birth weight for gestational age as

misclassified. Preterm delivery was defined as being born at <37 completed weeks of gestation.

Outcome

The outcome, chronic hypertension, was defined as blood pressure $\geq 140/90$ mmHg diagnosed before pregnancy, at first antenatal visit or before gestational week 20.¹⁷ Chronic hypertension was identified in early pregnancy by free text (1967-1998), which was later coded by MBRN using ICD-codes, or checkboxes (1999-2009) filled in by the midwife in Norway. In Sweden, the presence of chronic hypertension before pregnancy week 20 was identified by checkboxes filled in by the midwife and further recorded as a corresponding ICD-code, noted by the responsible doctor at discharge from the hospital after delivery (ICD-codes are provided in web appendix).

Covariates

Covariates used were country of origin (Norway/Sweden), age at delivery (<25, 25–29, ≥ 30 years), cohabitation (yes/no), level of education (≤ 12 , ≥ 13 years) and year of birth (<1975, 1975-1979, >1979) for the 2nd generation. In Sweden, solely marital status was recorded during the years 1973-81 (non-married cohabiting women were therefore defined as no cohabitation during these years). Thereafter, cohabitation included all women who lived together with their partner. Data on years of formal education by 2010 were obtained through linkage to the population-based education registers in each country, the Swedish Register of Education, a yearly updated register maintained by Statistics Sweden, and the Norwegian equivalent, the National Education Data Base, maintained by Statistics Norway.

The categorisation corresponds to the educational systems, where more than 12 years of education represents studies at college and university level.

In Swedish MBR, early pregnancy data on current smoking habits have been collected since 1983 and on body mass index (BMI) since 1992. Smoking was categorised as daily smoker and non-smoker, BMI was categorised as normal weight or underweight ($<25.0 \text{ kg/m}^2$), overweight ($25.0\text{-}29.9 \text{ kg/m}^2$), obesity class 1 ($30.0\text{-}34.9 \text{ kg/m}^2$) and obesity class 2-3 ($\geq 35 \text{ kg/m}^2$).

Statistical analysis

Risk of chronic hypertension in early pregnancy was first calculated for women with perinatal exposure to preeclampsia and to being born severe or moderate SGA, or preterm. The relative risk (RR) was calculated by log-binominal regression models. A directed acyclic graph (DAG) was created in order to select variables for the multivariable models (Supplemental Figure 1). The minimal sufficient set for confounder adjustment included age (1st generation) and socioeconomic factors (1st generation). We further adjusted for year of birth (2nd generation) and country of birth. Only study subjects without missing values of all covariates were included in the adjusted models. Multiplicative interaction between the three perinatal exposures was investigated by introducing cross-product terms between the exposures, by introducing them two at a time to the regression model. Further, to estimate additive interaction we calculated the relative excess risk due to interaction (RERI) with 95% confidence interval (CI). We created single and joint perinatal exposures to preeclampsia, being born SGA ($<10^{\text{th}}$ percentile) and being born preterm, and calculated the risk of getting chronic hypertension for each group. In total, 38,301 women were excluded from this

analysis due to missing data on birth weight or gestational age at birth. The common reference group was women without any of the perinatal exposures.

Smoking and BMI in the women of the 2nd generation might affect the outcome of the study.^{18, 19} However, both these covariates were only available in Sweden for women being pregnant in 1992 or later (n=397,063). In a supplementary analysis, we only included women from the Swedish MBR that gave birth in 1992 or later, where data on smoking habits as well as BMI were available (n=353,976). First, we adjusted for the same covariates from the 1st generation as above (age at delivery, cohabitation, years of formal education and year of birth); thereafter, in a second model we also included smoking habits and BMI in the 2nd generation as co-variables in the analysis.

RESULTS

Of the 731,008 primiparous women included in the study, 3161 were diagnosed with chronic hypertension (0.4%). The rate of chronic hypertension was lower among women born in Norway (0.3%) compared to women born in Sweden (0.5%). The rate of all three perinatal exposures was lower among the Norwegian than the Swedish women. The proportion of women born SGA was higher in the first part of the study period compared to the latter part of the period. The characteristics of the study population are summarised in Table 1.

Table 2 shows the risk of chronic hypertension by each perinatal exposure. In the first model, the risk was adjusted for potential confounders. In the second model, adjustment was also made for joint main exposures. The associations were slightly stronger before adjustment for joint exposure. Perinatal exposure to preeclampsia had the strongest association with

chronic hypertension, with a more than doubled risk. Compared with women not born SGA ($>10^{\text{th}}$ percentile), women born severe SGA ($<3^{\text{rd}}$ percentile) had a moderately increased risk of chronic hypertension (RR1.2 (95% CI 1.0, 1.4), but the risk of chronic hypertension was not associated with moderate SGA (3^{rd} to $<10^{\text{th}}$ percentile) (RR1.1 (95% CI 0.9, 1.3)). Women born preterm had 30% increased risk of chronic hypertension compared with women not born preterm. The risks of chronic hypertension showed a similar pattern after stratification for country of origin (Supplemental Table 1).

We could not show multiple interactions between the different exposures and the outcome: $P=0.5$ for interaction preeclampsia and SGA, $p=0.7$ for interaction preeclampsia and preterm born and $P=0.9$ for interaction SGA and preterm born. Nor interactions on the additive scale (RERI) were evident: 1.4 (95% CI -1.1, 3.8) for interaction preeclampsia and SGA, 0.3 (95% CI -0.9, 1.5) for interaction preeclampsia and preterm born and 0.5 (95% CI -0.4, 1.4) for interaction SGA and preterm born.

Table 3 presents the risk of chronic hypertension by single and joint perinatal exposure (with no exposure as the reference). Women exposed to any of the isolated exposures were associated with increased risk of chronic hypertension, and preeclampsia was the exposure resulting in the strongest association. Although there was no significant multiplicative or additive interaction between the exposures, the effect of the joint exposures showed a multiplicative pattern. The highest risk was noted after exposure to preeclampsia in coexistence with SGA or preterm delivery (RR 2.6, (95% CIs 1.7, 3.9) and RR 3.8, (95% CI 2.0, 7.0), respectively). Risk of chronic hypertension after presence of all three exposures simultaneously could not be correctly estimated due to sparse sample size.

Since BMI and smoking might be important confounders between the perinatal exposures and risk of chronic hypertension, we re-analysed our data in the subset from Sweden with available information on BMI and smoking from early pregnancy in the women of the 2nd generation. Further adjustments for BMI and smoking had only minor impact on our estimations, with slightly attenuated risk estimate for women with perinatal exposure to preeclampsia (Supplemental Table 2).

COMMENT

We found that perinatal exposure to preeclampsia, being born SGA and preterm were associated with increased risk of chronic hypertension in women by the time of their first pregnancy. Each exposure had an individual effect on the risk, with the strongest association after perinatal exposure to preeclampsia. Moreover, there was a conjoint effect of perinatal exposure to preeclampsia and being born SGA or preterm, with almost four-fold risk increase of chronic hypertension when women had reached fertile age.

Strengths and limitations

The major strength of our study was the size of the cohort with about 730 000 women followed from birth to pregnancy, which enabled the examination of single as well as joint exposures to preeclampsia, SGA, and preterm birth. Validity of data on gestational age and birth weight has been evaluated on a three graded scale as acceptable and good, respectively, in the Swedish MBR.²⁰ The accuracy of the preeclampsia diagnosis has been evaluated for the years 1987-1993 with a positive predictive value of 93% in Sweden ²¹ and 84% in Norway,²² and preterm birth has been evaluated with a positive predictive value of

93% in MBRN.²³ Furthermore, data were collected prospectively, which precludes recall bias, and the design was based on mandatory notification of all births in both countries, that minimises selection bias. Another strength was that we had data on important confounders, such as smoking and BMI. Further, chronic hypertension was recorded by a medical professional and hence, more reliable than if self-reported.

A limitation of the study is the shift in definition of chronic hypertension throughout the years of the study. However, the outcome was measured in the women of the 2nd generation, and recorded starting in the mid 80s. The diagnosis of chronic hypertension is not validated in the birth registers, which is another limitation. The rate of chronic hypertension in our study was 0.4%, which is low compared to a large number of prospective or cross-sectional studies.²⁴ Roberts and colleagues²⁵ found a marked under-reporting of chronic hypertension in register studies, which might explain the low prevalence in the study population. Women born severely small or preterm may suffer from sequelae such as impaired health, decreased fecundity or cognitive difficulties with the consequence that they never become mothers themselves. Thus, these results are only applicable to women with childbearing capacity. The two generation study design implies that the women of the 2nd generation are still in their fertile years. Further, the women of the 1st generation were included regardless of parity, while only primiparous women of the 2nd generation were included. Hence, skewness is present towards lower age in the 2nd generation, with 40% of women aged 25 years or younger; thereby, fewer women are expected to have developed chronic hypertension. In addition, if there is a misclassification of the outcome, it should be non-differential leading to an underestimation of the association. It is also possible that women with chronic hypertension are less likely to become pregnant due to ongoing

medication and cardiovascular complications; thus, the rate of chronic hypertension in the study population might be lower than in the whole population of women of fertile age.

There was a divergence in the rate of chronic hypertension between the two countries, which we believe is due to under-reporting of the diagnosis of chronic hypertension, as doctors at discharge from hospital do not diagnose chronic hypertension with ICD-codes after childbirth in Norway. However, when the results were stratified for country of origin, the pattern of risks of chronic hypertension were similar, even though the risks were not significant after exposure to SGA and preterm birth in Norway. Furthermore, we could not show an increased risk of chronic hypertension after joint exposure to all three scenarios, which we believe is a type II error due to a very rare exposure group. Likewise, the power to detect interaction was very low in the cases with all three exposures present simultaneously.

Comparisons with earlier studies

A large number of earlier studies on perinatal exposure to preeclampsia compared blood pressure levels in childhood or adolescence between exposed and unexposed individuals and hence, focused on blood pressure increases rather than chronic hypertension as outcome.^{26, 27} Chronic hypertension is more strongly associated with cardiovascular disease than slight elevations of blood pressure.²⁸ However, a majority of studies showed an association between perinatal exposure to preeclampsia and elevated blood pressure or hypertension later in life, which is in line with our findings. Palmsten and colleagues²⁹ reported an association between perinatal exposure to pregnancy-related hypertension and chronic hypertension later in life, but the risk estimate was essentially unchanged when birth weight and preterm birth was added in a multivariate model. However, their study was

smaller than ours with only 264 cases of self-reported diagnosed hypertension and the size of the cohort may have influenced the results.

A large body of evidence shows an association between low birth weight or preterm birth and increased risk of elevated blood pressure.¹¹ Nevertheless, the effects of low birth weight may be confounded by the effects of preterm birth, if not adjusted for gestational age.

Juonala and colleagues¹⁴ presented evidence on elevated blood pressure in childhood after preterm birth in children born SGA but not in preterm children with appropriate birth weight for gestational age, and the effect was more pronounced with increasing age at follow-up.

These findings indicate that there may be an additive effect of concurrent perinatal exposures, in line with our results.

Preeclampsia is often associated with IUGR, especially if the disease has early onset or is combined with preterm delivery.³⁰ Adjustment for co-existence of preeclampsia, IUGR and preterm birth is not always performed, and the effect of a single exposure can be exaggerated if not adjusted for conjoint exposures. Therefore, our study adds to existing knowledge by separating single and joint exposures in order to try to disentangle the effects of each separate perinatal exposure.

The association between perinatal exposure to preeclampsia, being born SGA or preterm and chronic hypertension in adult life might be explained by common genetics or lifestyle factors predisposing to both perinatal exposure and cardiovascular disease. Moreover, extensive evidence suggests that adverse effects and stimuli during foetal and early postnatal development can cause alterations in tissue structure and function as well as in

hormone balance and metabolism.^{8, 31-33} It is well-known that preeclampsia not only causes an inflammatory response, which is a major part of the atherosclerotic process, but also a change in the balance of placental growth factor and angiogenic factors, which may influence the development of the vascular tree.³⁴⁻³⁶ Furthermore, epigenetic mechanisms are thought to modify the growing vascular system after perinatal adverse events that affect endocrine and metabolic systems, e.g. the renin-angiotensin system, altering the control of fluid and electrolyte control, and the hypothalamic-pituitary-adrenal axis, resulting in increased response to stress.³⁷

The higher relative risk for combined exposure to preeclampsia and SGA or preterm birth may be explained by more severe preeclampsia than in the cases with preeclampsia without concurrent SGA or preterm birth. It is possible that severe preeclampsia involves an even higher inflammatory response, or additionally altered angiogenesis, and thereby an increased impact on the growing vascular tree.

In our study, chronic hypertension was more strongly associated with perinatal exposure to preeclampsia than being born SGA or preterm. Women who themselves have history of preeclampsia are 2 to 5 times more likely to develop cardiovascular disease or hypertension than women without history of preeclampsia.^{4, 5} We find it unlikely that life style factors are the major contributors to this association, as we were able to adjust for socioeconomic status, BMI and smoking. Instead, we suggest that the association is mainly mediated by common genetic factors, creating a vulnerability of the cardiovascular system possibly induced by epigenetic changes in the endocrine and inflammatory systems. Being born with low birth weight, including children born SGA as well as preterm, is associated with a

vascular system with structural and functional changes which might increase vulnerability even further and thus explain the increased risk estimate after joint exposure.³⁸

Growing evidence indicates that early and late preeclampsia, at least partly, have different aetiology and may be viewed as two different syndromes.³⁹ The American Heart Association acknowledges preeclampsia as a risk factor of future hypertension and cardiovascular disease in the mother,^{40,41} and the American Congress of Obstetricians and Gynecologists identifies preeclampsia with preterm birth as the high risk group in their guidelines.⁴² This study suggests that special attention should also be paid to the vascular health of the offspring.

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REFERENCES

1. A global brief on hypertension: silent killer, global public health crisis. Geneva: World Health Organization; 2013.
2. Shih PA, O'Connor DT. Hereditary determinants of human hypertension: strategies in the setting of genetic complexity. *Hypertension*. 2008 Jun;51(6):1456-1464.
3. Bonamy AK, Parikh NI, Cnattingius S, Ludvigsson JF, Ingelsson E. Birth characteristics and subsequent risks of maternal cardiovascular disease: effects of gestational age and fetal growth. *Circulation*. 2011 Dec 20;124(25):2839-2846.

4. Bellamy L, Casas JP, Hingorani AD, Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. *BMJ (Clinical Research ed)*. 2007 Nov 10;335(7627):974.
5. Smith GC, Pell JP, Walsh D. Pregnancy complications and maternal risk of ischaemic heart disease: a retrospective cohort study of 129,290 births. *Lancet*. 2001 Jun 23;357(9273):2002-2006.
6. Ferreira I, Peeters LL, Stehouwer CD. Preeclampsia and increased blood pressure in the offspring: meta-analysis and critical review of the evidence. *Journal of Hypertension*. 2009 Oct;27(10):1955-1959.
7. de Jong F, Monuteaux MC, van Elburg RM, Gillman MW, Belfort MB. Systematic review and meta-analysis of preterm birth and later systolic blood pressure. *Hypertension*. 2012 Feb;59(2):226-234.
8. Barker DJ, Thornburg KL. The obstetric origins of health for a lifetime. *Clinical Obstetrics and Gynecology*. 2013 Sep;56(3):511-519.
9. Norwitz ER. Defective implantation and placentation: laying the blueprint for pregnancy complications. *Reproductive Biomedicine Online*. 2006 Oct;13(4):591-599.
10. Whincup P, Cook D, Papacosta O, Walker M. Birth weight and blood pressure: cross sectional and longitudinal relations in childhood. *BMJ (Clinical Research ed)*. 1995 Sep 23;311(7008):773-776.
11. Mu M, Wang SF, Sheng J, Zhao Y, Li HZ, Hu CL, et al. Birth weight and subsequent blood pressure: a meta-analysis. *Archives of Cardiovascular Diseases*. 2012 Feb;105(2):99-113.
12. Eriksson J, Forsen T, Tuomilehto J, Osmond C, Barker D. Fetal and childhood growth and hypertension in adult life. *Hypertension*. 2000 Nov;36(5):790-794.
13. Bergvall N, Iliadou A, Tuvemo T, Cnattingius S. Birth characteristics and risk of high systolic blood pressure in early adulthood: socioeconomic factors and familial effects. *Epidemiology (Cambridge, Mass)*. 2005 Sep;16(5):635-640.
14. Juonala M, Cheung MM, Sabin MA, Burgner D, Skilton MR, Kahonen M, et al. Effect of birth weight on life-course blood pressure levels among children born premature: the Cardiovascular Risk in Young Finns Study. *Journal of Hypertension*. 2015 Aug;33(8):1542-1548.

15. Sarwar N, Gao P, Seshasai SR, Gobin R, Kaptoge S, Di Angelantonio E, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet*. 2010 Jun 26;375(9733):2215-2222.
16. Marsal K, Persson PH, Larsen T, Lilja H, Selbing A, Sultan B. Intrauterine growth curves based on ultrasonically estimated foetal weights. *Acta Paediatrica*. 1996 Jul;85(7):843-848.
17. RCOG. Hypertension in Pregnancy: The Management of Hypertensive Disorders During Pregnancy. Nice Clinical Guidelines. London: RCOG Press; 2010.
18. Rasmussen S, Irgens LM. The effects of smoking and hypertensive disorders on fetal growth. *BMC Pregnancy and Childbirth*. 2006;6:16.
19. Laura HC, Menezes AB, Noal RB, Hallal PC, Araujo CL. Maternal anthropometric characteristics in pregnancy and blood pressure among adolescents: 1993 live birth cohort, Pelotas, southern Brazil. *BMC Public Health*. 2010;10:434.
20. Cnattingius S, Ericson A, Gunnarskog J, Kallen B. A quality study of a medical birth registry. *Scandinavian Journal of Social Medicine*. 1990 Jun;18(2):143-148.
21. Ros HS, Cnattingius S, Lipworth L. Comparison of risk factors for preeclampsia and gestational hypertension in a population-based cohort study. *American Journal of Epidemiology*. 1998 Jun 1;147(11):1062-1070.
22. Klungsoyr K, Harmon QE, Skard LB, Simonsen I, Austvoll ET, Alsaker ER, et al. Validity of pre-eclampsia registration in the medical birth registry of Norway for women participating in the Norwegian mother and child cohort study, 1999-2010. *Paediatric and Perinatal Epidemiology*. 2014 Sep;28(5):362-371.
23. Moth FN, Sebastian TR, Horn J, Rich-Edwards J, Romundstad PR, Asvold BO. Validity of a selection of pregnancy complications in the Medical Birth Registry of Norway. *Acta Obstetrica et Gynecologica Scandinavica*. 2016 May;95(5):519-527.
24. Vest AR, Cho LS. Hypertension in pregnancy. *Current Atherosclerosis Reports*. 2014 Mar;16(3):395.
25. Roberts CL, Bell JC, Ford JB, Hadfield RM, Algert CS, Morris JM. The accuracy of reporting of the hypertensive disorders of pregnancy in population health data. *Hypertension in Pregnancy*. 2008;27(3):285-297.

26. Oglænd B, Forman MR, Romundstad PR, Nilsen ST, Vatten LJ. Blood pressure in early adolescence in the offspring of preeclamptic and normotensive pregnancies. *Journal of Hypertension*. 2009 Oct;27(10):2051-2054.
27. Vatten LJ, Romundstad PR, Holmen TL, Hsieh CC, Trichopoulos D, Stuver SO. Intrauterine exposure to preeclampsia and adolescent blood pressure, body size, and age at menarche in female offspring. *Obstetrics and Gynecology*. 2003 Mar;101(3):529-533.
28. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet*. 2002 Dec 14;360(9349):1903-1913.
29. Palmsten K, Buka SL, Michels KB. Maternal pregnancy-related hypertension and risk for hypertension in offspring later in life. *Obstetrics and Gynecology*. 2010 Oct;116(4):858-864.
30. Ananth CV, Peedicayil A, Savitz DA. Effect of hypertensive diseases in pregnancy on birthweight, gestational duration, and small-for-gestational-age births. *Epidemiology (Cambridge, Mass)*. 1995 Jul;6(4):391-395.
31. Osterholm EA, Hostinar CE, Gunnar MR. Alterations in stress responses of the hypothalamic-pituitary-adrenal axis in small for gestational age infants. *Psychoneuroendocrinology*. 2012 Oct;37(10):1719-1725.
32. Jayet PY, Rimoldi SF, Stuber T, Salmon CS, Hutter D, Rexhaj E, et al. Pulmonary and systemic vascular dysfunction in young offspring of mothers with preeclampsia. *Circulation*. 2010 Aug 3;122(5):488-494.
33. Jensen RB, Chellakooty M, Vielwerth S, Vaag A, Larsen T, Greisen G, et al. Intrauterine growth retardation and consequences for endocrine and cardiovascular diseases in adult life: does insulin-like growth factor-I play a role? *Hormone Research*. 2003;60 Suppl 3:136-148.
34. van Rijn BB, Bruinse HW, Veerbeek JH, Post Uiterweer ED, Koenen SV, van der Bom JG, et al. Postpartum Circulating Markers of Inflammation and the Systemic Acute-Phase Response After Early-Onset Preeclampsia. *Hypertension*. 2016 Feb;67(2):404-414.
35. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. *Circulation*. 2002 Mar 5;105(9):1135-1143.
36. Conti E, Zezza L, Ralli E, Caserta D, Musumeci MB, Moscarini M, et al. Growth factors in preeclampsia: a vascular disease model. A failed vasodilation and angiogenic

challenge from pregnancy onwards? *Cytokine & Growth Factor Reviews*. 2013 Oct;24(5):411-425.

37. O'Sullivan L, Combes AN, Moritz KM. Epigenetics and developmental programming of adult onset diseases. *Pediatric Nephrology (Berlin, Germany)*. 2012 Dec;27(12):2175-2182.

38. Norman M. Low birth weight and the developing vascular tree: a systematic review. *Acta Paediatrica*. 2008 Sep;97(9):1165-1172.

39. Verlohren S, Melchiorre K, Khalil A, Thilaganathan B. Uterine artery Doppler, birth weight and timing of onset of pre-eclampsia: providing insights into the dual etiology of late-onset pre-eclampsia. *Ultrasound in Obstetrics & Gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology*. 2014 Sep;44(3):293-298.

40. Bushnell C, McCullough LD, Awad IA, Chireau MV, Fedder WN, Furie KL, et al. Guidelines for the prevention of stroke in women: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke; a Journal of Cerebral Circulation*. 2014 May;45(5):1545-1588.

41. Pariente G, Shoham-Vardi I, Kessous R, Sherf M, Sheiner E. Placental abruption as a significant risk factor for long-term cardiovascular mortality in a follow-up period of more than a decade. *Paediatric and Perinatal Epidemiology*. 2014 Jan;28(1):32-38.

42. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. *Obstetrics and Gynecology*. 2013 Nov;122(5):1122-1131.

Table 1

Characteristics of study population in relation to perinatal exposures

Characteristics	Perinatal exposures							
	Preeclampsia		Born SGA		Born preterm		Unexposed	
	n	%	n	%	n	%	n	%
Country of origin								
Sweden	8267	55.1	37,431	52.9	16,585	57.4	340,469	54.6
Norway	6735	44.9	33,358	47.1	12,316	42.6	283,725	45.4
Age 1st generation (years)								
<25	6825	45.5	35,450	50.1	13,370	46.3	262,927	42.1
25-29	4417	29.4	22,007	31.1	8418	29.1	215,719	34.6
≥30	3760	25.1	13,332	18.8	7113	24.6	145,548	23.3
Cohabitation 1st generation								
Yes	11,096	74.0	49,471	69.9	20,316	70.3	480,337	77.0
No	3120	20.8	17,693	25.0	6764	23.4	113,159	18.1
Missing data	786	5.2	3625	5.1	1821	6.3	30,698	4.9
Education 1st generation (years)								
≤12	11,333	75.5	55,029	77.8	22,325	77.2	460,842	73.8
≥13	3160	21.1	12,833	18.1	5274	18.3	145,934	23.4
Missing data	509	3.4	2927	4.1	1302	4.5	17,418	2.8
Age 2nd generation (years)								
<25	6331	42.2	30,841	43.6	12,516	43.3	250,414	40.1
25-29	5712	38.1	25,385	35.8	10,579	36.6	238,421	38.2
≥30	2959	19.7	14,563	20.6	5806	20.1	135,359	21.7
Cohabitation 2nd generation								
Yes	12,855	85.7	59,478	84.0	24,342	84.2	538,187	86.2
No	1725	11.5	9146	12.9	3648	12.6	67,601	10.8
Missing data	422	2.8	2165	3.1	911	3.2	18,406	2.9
Education 2nd generation (years)								
≤12	8227	54.8	42,027	59.4	16,929	58.6	329,403	52.8
≥13	6713	44.7	28,403	40.1	11,817	40.9	292,179	46.8
Missing data	62	0.4	359	0.5	155	0.5	2612	0.4
Year of birth 2nd generation								
<1975	4785	31.9	28,487	40.2	10,255	35.5	232,129	37.2
1975-1979	4734	31.6	23,524	33.2	9022	31.2	202,216	32.4
>1979	5483	36.5	18,778	26.5	9624	33.3	189,849	30.4
Total	15,002		70,789		28,901		624,194	

SGA, small for gestational age.

Table 2

Risk of chronic hypertension in primiparous women by perinatal exposure at own birth.

Perinatal exposure	Chronic hypertension				
	Total	Number of cases	Risk (%)	Relative risk ^b (95% confidence interval)	
				Model 1 ^b	Model 2 ^c
Preeclampsia					
Yes	15,002	146	1.0	2.3 (1.9, 2.7)	2.2 (1.8, 2.6)
No	716,006	3015	0.4	1.0 (Reference)	1.0 (Reference)
Standardised birth weight^a					
<3 rd percentile	21,471	113	0.5	1.2 (1.0, 1.4)	1.2 (1.0, 1.4)
3 rd to <10 th percentile	49,318	249	0.5	1.2 (1.0, 1.4)	1.1 (0.9, 1.3)
≥10 th percentile	641,124	2732	0.4	1.0 (Reference)	1.0 (Reference)
Missing data	19,095	67	0.4		
Preterm (<37 weeks)					
Yes	28,901	168	0.6	1.3 (1.1, 1.6)	1.3 (1.1, 1.6)
No	685,557	2938	0.3	1.0 (Reference)	1.0 (Reference)
Missing data	16,550	55	0.3		

^aStandardised birth weight: deviation from expected mean weight for gestational age, according to the Swedish sex-specific foetal growth curve

^b Model 1 is adjusted for country of origin, age at delivery 1st generation, cohabitation or not 1st generation, years of formal education 1st generation and year of birth 2nd generation

^c Model 2 is adjusted for all variables as in Model 1, but also for the other main exposures listed in the table

Table 3

Risk of chronic hypertension in primiparous women by perinatal exposures. This table only includes women with known exposure data (n=711,913).

Perinatal exposure				Chronic hypertension		
Preeclampsia	SGA (<10 th percentile)	Preterm birth	Total women	Number of cases	Risk (%)	Relative risk (95% confidence interval)
No	No	No	606,903	2505	0.4	1.0 (Reference)
Yes	No	No	10,554	96	0.9	2.2 (1.8, 2.7)
No	Yes	No	64,568	303	0.5	1.1 (1.0, 1.3)
No	No	Yes	22,895	118	0.5	1.3 (1.0, 1.5)
Yes	Yes	No	2385	28	1.2	2.6 (1.7, 3.9)
Yes	No	Yes	772	13	1.7	3.8 (2.0, 7.0)
No	Yes	Yes	3007	26	0.9	1.9 (1.2, 3.0)
Yes	Yes	Yes	829	5	0.6	1.8 (0.7, 4.2)

Relative risks are adjusted for country of origin, age at delivery 1st generation, cohabitation or not 1st generation, years of formal education 1st generation and year of birth 2nd generation