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## Chronic Hypertension Related to Risk for Preterm and Term Small-for-Gestational-Age Births

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### Abstract

**Objective:** Evidence relating chronic hypertension to risk of small for gestational age (SGA) births is conflicting. To identify factors associated with SGA that may involve a placental pathogenesis, we related chronic hypertension and other maternal factors that may be markers of endothelial dysfunction to preterm compared with term SGA births.

**Methods:** Chronic hypertension, diabetes, body mass index, age, and subfertility were related to risk of term and preterm SGA births in the Danish National Birth Cohort (n=81,008). SGA births were those with a birth weight adjusted for gestational age greater than 2 standard deviations below the mean based on fetal growth curves.

**Results:** Risk of preterm SGA increased 5.5-fold (95% CI 3.2-9.4) and risk of term SGA increased 1.5-fold (1.0-2.2) among women with definite chronic hypertension. Risk of preterm SGA but not term SGA was increased among women less than 20 (odds ratio [OR] 2.8, 95% CI: 1.1-6.8) or greater than 36 (OR 2.0, 95% CI: 1.3-3.1) years of age and among those with at least 2 early spontaneous abortions (OR 2.0, CI: 1.3-3.3). Smoking, parity, time to pregnancy greater than 12 months, and underweight status were similarly related to term and preterm SGA. Overweight status, obesity, and presence of diabetes were unrelated to either SGA subtype.

**Conclusions:** Chronic hypertension, young or older maternal age, and recurrent early spontaneous abortions increased risk for preterm SGA. These factors may involve abnormal placentation and likely represent a pathogenesis distinct from that leading to term SGA.

### INTRODUCTION

Growth restriction, typically measured as weight or other markers of fetal growth that are small for gestational age (SGA), is detectable early in pregnancy. (1) A portion of SGA cases with and without preeclampsia are associated with endothelial dysfunction leading to abnormal placentation. (2,3) Pre-existing maternal factors that predispose to preeclampsia may therefore also be risk factors for SGA. Women without preeclampsia who deliver growth restricted neonates in a first pregnancy are 3 times more likely to have preeclampsia in a second pregnancy. (4) In addition, women who deliver small babies or have pregnancies complicated

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by preeclampsia are at increased risk for cardiovascular disease later in life.(5-8) Smaller babies themselves also have increased risk for chronic disease later in life, (9-11) raising the possibility that the association between infant birth weight and later life morbidity may well be secondary to the underlying causes of fetal growth restriction.

Some studies have reported that chronic hypertension, a clinical manifestation of endothelial dysfunction, increases risk for SGA. (12,13) However, a recent large international study indicated that SGA and preeclampsia had distinct patho-physiologies, a conclusion driven dominantly by the finding that chronic hypertension was unrelated to SGA risk. (14)

We used data from a large, well characterized cohort of women with singleton pregnancies not complicated by preeclampsia to examine if chronic hypertension and other factors that could be intermediary between endothelial dysfunction and SGA (diabetes, BMI, and subfertility) were related to risk for term and preterm SGA. We hypothesized that pre-existing factors related to endothelial dysfunction would have a more profound effect on preterm SGA vs. term SGA as these cases likely involve a placental pathogenesis. Additionally, we asked if these measures of association might differ in smokers and non-smokers given their very different background risk for SGA.

## MATERIALS AND METHODS

The Danish National Birth Cohort is a longitudinal study of pregnant women and their offspring approved by the Danish Ethics Central Committee. Details regarding recruitment, retention and data collection have been published.(15,16) Women were approached by their general practitioner at the first antenatal care visit, and about 50% of all general practitioners in Denmark participated in the recruitment from 1996 to 2002. Of those women invited to participate, about 60% consented and were interviewed twice during pregnancy and twice after delivery. This study combines information from the first three interviews with data from the National Birth Register and the National Hospital Discharge Register by means of a unique personal code given to each citizen in Denmark.

Of all pregnant women recruited to the Danish National Birth Cohort (n=101,033), we identified 85,645 women with singleton pregnancies who completed the first interview and delivered live born ( $\geq 24$  weeks) infants without congenital malformations. In order to study the effects of factors related to SGA risk separate from those mediated by preeclampsia, women with definite (based on ICD-10 codes, n=2386) or possible preeclampsia (based on self-report, n=807) were excluded. We also excluded women with one or more missing study variables (n=1,444); these women had rates of SGA similar to the final study population (n=81,008; 2.3% and 2.2%, respectively, p=0.77).

Women were categorized with definite hypertension if they reported ever having chronic hypertension at the first interview (completed at median of 16 weeks, range 7-40 weeks; interquartile range 13-19 weeks) and also reported taking antihypertensive medication or indicated that they still suffered from hypertension. Those who reported a history of chronic hypertension but who were not on medication or indicated that they no longer had hypertension were classified with probable hypertension. Height and pre-pregnancy weight (used to calculate body mass index [BMI],  $\text{kg}/\text{m}^2$ ) were also reported during this first interview. BMI was categorized as underweight ( $<18.5$ ), normal weight (18.5-24.9), overweight (25-29.9), and obese ( $\geq 30$ ).(17) Pre-existing diabetes was assessed during the second interview (median of 31 weeks, interquartile range 29-33 weeks), and was supplemented with cases identified via ICD-10 diagnostic codes for insulin dependent or non-insulin dependent diabetes occurring in the National Hospital Discharge Register prior to the estimated date of conception. We also identified cases of gestational diabetes (n=798) in the National Hospital Discharge Register or

from self-report in the interviews as this disease has pre-existing characteristics consistent with the metabolic syndrome. (18) Results were unchanged when women with pre-existing and gestational diabetes were combined, so we reported estimates associated with the combined group.

We also considered reproductive history as a preexisting condition that may be related to SGA risk via endothelial dysfunction and early placentation abnormalities.(19) Number of previous births as well as number and gestational age of spontaneous abortions (<12 weeks and  $\geq$ 12 weeks) were reported at the first interview. Women who reported that their pregnancy was fully or partly planned (89%) also reported waiting time to pregnancy (TTP). TTP  $\geq$  12 months was considered an indicator of subfertility; unplanned pregnancies and those occurring before 12 months of trying to conceive were the referent.

The main outcome was SGA, defined according to the criteria of Marsal et al as birth weight >2 SD below the mean for a given gestational age based on fetal weights derived from serial ultrasounds among a Scandinavian population. (20) This was further divided into term SGA ( $\geq$ 37 weeks) and preterm SGA (<37 weeks) to describe severity. Gestational age was based on the best clinical estimate at birth, which in more than 90% of cases was checked and adjusted according to early ultrasound. (21) When missing (n=862), the estimate of gestational age was based on a woman's last menstrual period, reported at recruitment. Mean gestational age in the cohort was 39.6 weeks (range 24-45 weeks).

Self-reported information about smoking status and number of cigarettes smoked came from the first and second interviews. The rates of SGA births among non-smokers and women that quit smoking during pregnancy were similar (1.6% vs. 1.8%, p= 0.16). Therefore these two groups were combined into non-smokers, while smokers were defined as those women who reported smoking at the first and second interviews. When the second interview was missing (n=6,078), smokers were identified from the first interview.

Maternal age at delivery was also considered as a possible determinant of SGA risk that may be related to endothelial dysfunction. Socio-occupational status was considered as a confounder, and was based on a woman's current or most recent job (within 6 months) or on the type of education for women who reported being in school. The category of high socio-occupational status included women in management or those with jobs requiring more than 4 years of education beyond high school. Office, service, or skilled manual workers and women in the military were classified in the middle category; unskilled workers or unemployed women were classified in the low category. Women who could not be classified (4%) were categorized according to their husband's socio-occupational status.

Maternal characteristics according to SGA status (non-SGA, term SGA, preterm SGA) were compared using chi square tests. Polytomous logistic regression models (22) were used to estimate the risk of term and preterm SGA according to pre-existing conditions while adjusting mutually for all factors studied and with additional adjustment for socio-occupational status and height. These models were built with robust standard errors after clustering on the individual woman to allow for women to contribute more than one observation (n=5175) without underestimating the true variance. SAS PROC SURVEYLOGISTIC was used for these models. (23) We tested if the effect of pre-existing conditions was equivalent between term and preterm SGA subtypes using a Wald-type test.(24) We also tested if the relative association between each pre-existing condition and SGA was modified by smoking or parity status (nulliparity vs. multiparity) using a likelihood-ratio-like test.(24) Significance level for all tests was 0.05, and SAS 9.1 was used for all analyses.(25)

## RESULTS

A total of 1,752 infants were identified as SGA (2.2%), and 13% of these were also preterm. Overall, 1.9% of infants were term SGA and 0.3% were preterm SGA. When compared to women with non-SGA infants, women with term or preterm SGA infants were more likely to be younger than 20 years of age or older than 36, of low socio-occupational status, to be smokers, to have probable or definite hypertension, to be underweight, to be nulliparous, or to have a time to pregnancy of  $\geq 12$  months (Table 1).

A total of 975 women reported definite hypertension (1.2%). When adjusted for age, BMI, diabetes, parity, smoking and subfertility, definite hypertension was associated with a 5.5-fold increased risk for preterm SGA (95% CI: 3.2,9.4) and definite or probable hypertension conferred a 1.5 to 1.7-fold increase in risk for term SGA (Table 2). Women with 2 or more spontaneous abortions before 12 weeks gestation had a 2-fold increased risk for preterm SGA (95% CI 1.3,3.3); there was no relation to term SGA. Maternal age  $< 20$  was related to risk for preterm SGA (OR 2.8, 95% CI: 1.1,6.8) but not term SGA. Similarly, maternal age  $\geq 36$  years was related to preterm SGA risk (OR 2.0, 95% CI: 1.3,3.1), but the effect was more modest for term SGA (OR 1.2, 95% CI: 1.0-1.5).

Maternal smoking conferred a 3-fold increase in risk for both term and preterm SGA, and multiparous women had a reduced risk for both SGA subtypes. Time to planned pregnancy (TTP) of more than 12 months was associated with a 30 to 40% increased risk for both term and preterm SGA. Maternal underweight (BMI  $< 18.5$  kg/m<sup>2</sup>) was associated with increased risk for both term (OR 1.6, 95% CI 1.3,1.9) and preterm SGA (OR 2.0, 95% CI 1.2,3.1), but there was no relation between overweight or obesity and SGA risk. The presence of diabetes was not related to risk of SGA.

We detected effect measure modification by smoking for age and SGA ( $p < 0.01$ ) as well as for time to planned pregnancy and SGA ( $p = 0.04$ ). The absolute risk of SGA according to each pre-existing factor studied was higher among smokers compared to non-smokers, although for most factors the magnitudes of the relative risks were similar. Some differences, however, emerged. For example, smokers  $\geq 36$  years of age had a 2-fold increased risk for SGA (95% CI: 1.5,2.5) compared to smokers age 26 to 30, whereas no difference in risk was observed between these two age groups among non-smokers. In contrast, non-smokers  $< 20$  years of age had a 1.9-fold increased risk (95% CI: 1.0,3.5) compared to the non-smoking referent group, while no difference in risk between these two groups was observed among smokers. A history of 2 or more spontaneous abortions before 12 weeks gestation or TTP  $> 12$  months conferred a 40% to 60% increased risk of SGA among non-smokers, whereas there was no effect of these factors on SGA risk among smokers.

There was no evidence of effect measure modification by parity status for any pre-existing factors and SGA.

## DISCUSSION

Our results suggest that chronic hypertension is a strong determinant of preterm SGA, independent of other factors, including maternal age, BMI, parity, and smoking status. Young and older maternal ages as well as recurrent early spontaneous abortions also conferred increased risk for preterm SGA, with modest or no effects on term SGA risk. These factors may involve an inadequate vascular response to pregnancy associated with abnormal placentation and may represent a pathogenesis distinct from that leading to term SGA.

An association between chronic hypertension and SGA risk has been reported in smaller studies (12,13) but Villar et al, recently reported no increased risk for SGA among non-smoking women

with chronic hypertension.(14) The reason could be that his study was carried out in developing countries where other risk factors may be more important such as poor nutrition or infection (26) . Kramer, et al reported that chronic hypertension was related to both term and preterm SGA among a large hospital-based cohort in Canada using birth weight growth standards(27) but it is well accepted that preterm birth weights do not represent the weight of the entire fetal population. The reason for being born preterm may well impact fetal growth.(20,28,29)

The evidence relating young or older maternal age to SGA risk has been conflicting, perhaps due to the heterogenous nature of SGA.(27,30) Our data indicate that the effects of both young and old age are dominantly related to preterm SGA risk. It is likely that older age affects the ability of the maternal vasculature to adequately adapt to the demands of pregnancy and placentation, resulting in decreased placental perfusion.(31) Results for women <20 years of age may be confounded by unmeasured social factors since many risk factors for SGA cluster in young pregnant women.(32) However, it is also possible that implantation and placentation may be compromised in young woman due to biologic immaturity, perhaps when combined with poor nutritional status.(33)

There is evidence that subfertility, or the causes of subfecundity, are associated with adverse pregnancy outcomes, including preterm birth (34-36), perinatal loss (37), preeclampsia (38) and small for gestational age births.(34-37) Our results extend this by providing evidence that recurrent early pregnancy losses were associated with increased risk of preterm but not term SGA; a long waiting time to pregnancy was related to preterm and term SGA. Thus, placental dysfunction may be implicated in some cases of SGA related to subfecundity but this warrants further study. Our data also provide intriguing evidence that subfertility may interact with smoking status such that risk of SGA is elevated only among non-smokers. It is possible that the profound effects of smoking eclipse the perhaps more subtle relationship of other factors on risk for SGA. Alternatively, smoking may be on the causal pathway, or be a collider, in the paths leading to subfertility,(39) early spontaneous pregnancy loss, (40-42) as well as SGA.

Our finding that smoking, parity and underweight status have similar effects on both term and preterm SGA suggest that these factors likely influence fetal growth in the second half of pregnancy. While vascular capacity expands dramatically in the first 20 weeks of pregnancy, nutritional needs are paramount later in gestation. (43) Our results suggest that smoking, parity and underweight status may affect the maternal capacity to provide adequate nutritional substrate to meet the large cell division that occurs in the second and third trimester.

We have previously reported that chronic hypertension conferred a 3.4-fold increase in risk of preeclampsia among nulliparous women, and risk of preterm preeclampsia increased 5.4-fold. (44) Here we show a similar 5-fold elevation among women with definite hypertension for preterm SGA. Taken together, these results demonstrate a strong and convincing relationship between chronic hypertension and risk for both preeclampsia and SGA, especially for the more severe subtypes of each condition. We also found that, in contrast to preeclampsia, SGA risk was inversely related to BMI providing support for the possibility that in the presence of more profound vascular damage, high BMI may predispose to preeclampsia. (45)

Important strengths of our study include the large and well-characterized nature of the Danish National Birth Cohort that allows for investigation of relatively rare pregnancy outcomes, such as term and preterm SGA. The cohort was established within a tax paid public health care system where more than 99% of women access prenatal care and where standardized and validated diagnostic as well as outcome information are available in national registers.(15, 46)

Limitations to our study include the fact that the majority of the population in Denmark is caucasian, and results may well be different in other ethnic groups. We relied on self-report of

some study variables, although we validated these data with diagnostic or other confirmatory information when available. For example, self-reported pre-existing hypertension was classified as definite when women also reported taking anti-hypertensive medication and there was high agreement between self-reported abortion information when compared to those in the Hospital Discharge Register. However, we were unable to evaluate actual blood pressure measures. Although we were not able to distinguish cases of transient hypertension during pregnancy, the link between this pregnancy complication and SGA risk is equivocal making it an unlikely source of confounding. BMI was based on self-reported height which tends to be overestimated, and self-reported weight which tends to be underestimated. (47) Despite this, a validation study of over 5000 women in the DNBC indicated that 91.4% of women were allocated to the appropriate BMI category based on self-reported height and weight suggesting any bias in these data is minimal. (48)

Our results indicated that chronic hypertension without superimposed preeclampsia increased the risk of preterm SGA substantially. In addition, young or older maternal age and recurrent early spontaneous abortions increased risk for preterm SGA, suggesting that these factors may disrupt fetal growth very early in gestation perhaps due to abnormal placentation. In contrast, smoking, parity and low maternal pre-pregnancy BMI had similar effects on preterm and term SGA suggesting a later pregnancy pathogenesis.

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## References

1. Smith G, Stenhouse E, Crossley J, Aitken D, Cameron A, Connor J. First-trimester growth and the risk of low birth weight. *N Engl J Med* 1998;339:1817–22. [PubMed: 9854117]
2. Kaufmann P, Black S, Huppertz B. Endovascular Trophoblast Invasion: Implications for the Pathogenesis of Intrauterine Growth Retardation and Preeclampsia. *Biol Reprod* July 1;2003 69(1): 1–7. [PubMed: 12620937]2003
3. Sheppard B, Bonnar J. Uteroplacental hemostasis in intrauterine fetal growth retardation. *Seminars in Thrombosis and Hemostasis* 1999;25(5):443–6.
4. Rasmussen S, Irgens L, Albrechtsen S, Kalaker K. Predicting preeclampsia in the second pregnancy from low birth weight in the first pregnancy. *Obstet Gynecol* 2000;96:696–7000. [PubMed: 11042303]
5. Smith G, Pell J, Walsh D. Pregnancy complications and maternal risk of ischaemic heart disease: a retrospective cohort study of 129,290 births. *Lancet* 2001;357(9273):2002–6. [PubMed: 11438131]
6. Davey Smith G, Harding S, Rosato M. Relation between infants' birth weight and mothers' mortality: prospective observational study. *BMJ* 2000;320(7238):839–40. [PubMed: 10731177]
7. Davey Smith G, Whitley E, Gissler M, Hemminki E. Birth dimensions of offspring, premature birth, and the mortality of mothers. *Lancet* 2000;356:2066–67. [PubMed: 11145495]
8. Davey Smith G, Sterne J, Tynelius P, Lawlor D, Rasmussen F. Birth weight of offspring and subsequent cardiovascular mortality of the parents. *Epidemiology* 2005;16(4):563–9. [PubMed: 15951676]
9. Leon D, Lithell H, Vagero D, Koupirova I, Mohsen R, Lithell U, et al. Reduced fetal growth rate and increased risk of death from ischaemic heart disease: cohort study of 15000 Swedish men and women born 1915–29. *BMJ* 1998;317:241–4. [PubMed: 9677213]
10. Barker D, Osmond C. Infant mortality, childhood nutrition, and ischaemic heart disease in England and Wales. *Lancet* 1986;8489(1):1077–81. [PubMed: 2871345]
11. Barker D. The fetal origins of coronary heart disease. *Acta Paediatr* 1997;422(Supplement):S78–S82.

12. Scott A, Moar V, Ounsted M. The relative contributions of different maternal factors in small-for-gestational-age pregnancies. *European Journal of Obstetrics & Gynecology and Reproductive Biology* 1981;12(3):157–65. [PubMed: 7197640]1981
13. Haelterman E, Breart G, Paris-Liado J, Dramaix M, Tchobroutsky C. Effect of Uncomplicated Chronic Hypertension on the Risk of Small-for-Gestational Age Birth. *Am J Epidemiol* April 15;1997 145(8):689–95. [PubMed: 9125995]1997
14. Villar J, Carroli G, Wojdyla D, Abalos E, Giordano D, Ba'aqeel H, et al. Preeclampsia, gestational hypertension and intrauterine growth restriction, related or independent conditions? *American Journal of Obstetrics and Gynecology* 2006;194(4):921–31. [PubMed: 16580277]2006
15. Olsen J, Melbye M, Olsen S, sorensen T, Aabay P, Andersen A, et al. The Danish National Birth Cohort-its background, structure and aim. *Scand J Public Health* 2001;29:300–7. [PubMed: 11775787]
16. www.bsmb.dk. [cited; Available from:
17. WHO Consultation on Obesity. Obesity: Preventing and Managing the Global Epidemic. 2000WHO Technical Report Series 894
18. Jovanovic L, Pettitt DJ. Gestational Diabetes Mellitus. *JAMA* 2001;286(20):2516–8. [PubMed: 11722247]
19. Zhu JL, Obel C, Hammer Bech B, Olsen J, Basso O. Infertility, Infertility Treatment, and Fetal Growth Restriction 2007:1326–34.
20. Marsal K, Persson PH, Larsen T, Lilja H, Selbing A, Sultan B. Intrauterine growth curves based on ultrasonically estimated foetal weights 1996:843–8.
21. Jorgensen F. Ultrasonography of pregnant women in Denmark 1999-2000: Description of the development since 1980-1990. *Ugeskr Laeger* 2003;165:4409–15. [PubMed: 14655565]
22. Hosmer, D.; Lemeshow, S. *Applied Logistic Regression*. Second ed.. John Wiley & sons, Inc; New York: 2000.
23. Williams RL. A Note on Robust Variance Estimation for Cluster-Correlated Data. *Biometrics* 2000;56 (2):645–6. [PubMed: 10877330]
24. Hardin, J.; Hilbe, J. *Generalized Estimating Equations*. Chapman & Hall/CRC; Boca Raton: 2003.
25. SAS. 9.1 ed.. SAS Institute, Inc; Cary, NC: 20022003.
26. Robinson J, Moore V, Owens J, Mcmillen C. Origins of fetal growth restriction. *European Journal of Obstetrics & Gynecology and Reproductive Biology* 2000;92:13–9. [PubMed: 10986429]
27. Kramer MS, Platt R, MSc HY, McNamara H, Usher RH. Are All Growth-restricted Newborns Created Equal(ly)? *Pediatrics* March 1;1999 103(3):599–602. [PubMed: 10049963]1999
28. Morken N-H, Kallen K, Jacobsson B. Fetal growth and onset of delivery: A nationwide population-based study of preterm infants. *Am J Obstet Gynecol* 2006;195(1):154–61. [PubMed: 16813752] 2006
29. Zeitlin J, Ancel PY, Saurel-Cubizolles MJ, Papiernik E. The relationship between intrauterine growth restriction and preterm delivery: an empirical approach using data from a European case-control study 2000:750–8.
30. Kramer, MS. Determinants of low birth weight: methodological assessment and meta-analysis. 65. *Bulletin of the World Health Organization*; 1987. p. 663-737.
31. Naeye R. Maternal age, obstetric complications, and the outcome of pregnancy. *Obstet Gynecol* 1983;61:210–6. [PubMed: 6823362]
32. Scholl T, Heideger M, Huang J, Johnson F, Smith W, Ances I. Young maternal age and parity. Influences on pregnancy outcome. *Ann Epidemiol* 1992;2(5):565–75. [PubMed: 1342308]
33. Wallace J, Bourke D, DaSilva P, Aitken D. Nutrient partitioning during adolescent pregnancy. *Reproduction* 2001;122(34757)
34. Basso O, Baird D. Infertility and preterm delivery, birthweight, and Caesarean section: a study within the Danish National Birth Cohort. *Hum Reprod* 2003;18(11):2478–84. [PubMed: 14585905]
35. Basso O, Olsen J, Christensen K. Risk of preterm delivery, low birthweight and growth retardation following spontaneous abortion: a registry-based study in Denmark. *Int J Epidemiol* 1998;27 (642646)

36. Tulppala M, Palosuo, Ramsay T, Miettinen A, Salonen R, Ylikorkala O. A prospective study of 63 couples with a history of recurrent spontaneous abortion: contributing factors and outcome of subsequent pregnancies. *Hum Reprod* 1993;8(5):764–70. [PubMed: 8314975]
37. Jivraj S, Anstie B, Cheong Y-C, Fairlie FM, Laird SM, Li TC. Obstetric and neonatal outcome in women with a history of recurrent miscarriage: a cohort study. *Hum Reprod* January 1;2001 16(1): 102–6. [PubMed: 11139545]2001
38. Basso O, Weinber C, Baird D, Wilcox A, Olsen J. Subfecundity as a correlate of preeclampsia: a study within the Danish National Birth Cohort. *Am J Epidemiol* 2003;157:195–202. [PubMed: 12543618]
39. Practice Committee of the American Society for Reproductive Medicine. Smoking and infertility. *Fertility and Sterility* 2004;81(4):1181–6. [PubMed: 15066502]
40. Ness RB, Grisso J, Hirschinger N, Markovic N, Shaw L, Day N, et al. Cocaine and tobacco use and the risk of spontaneous abortion. *N Engl J Med* 1999;340:333–9. [PubMed: 9929522]
41. Armstrong B, McDonald A, Sloan M. Cigarette, alcohol, and coffee consumption and spontaneous abortion. *American Journal of Public Health* 1992;82:85–7. [PubMed: 1536340]
42. Windham G, Swan S, Fenster L. Parental cigarette smoking and the risk of spontaneous abortion. *American Journal of Epidemiology* 1992;135:1394–403. [PubMed: 1510085]
43. Nuwayhid, B.; Nguyen, T.; Khraibi, A. Maternal physiology. In: Hacker, N.; Moore, J., editors. *Essentials of Obstetrics and Gynecology*. Third ed.. W.W. Saunders Company; Philadelphia: 1998.
44. Catov J, Ness R, Kip K, Olsen J. Risk of early or severe preeclampsia related to preexisting conditions. *Int J Epidemiol* 2007;36(2):412–9. [PubMed: 17255351]
45. Ness R, Sibai B. Shared and disparate components of the pathophysiologies of fetal growth restriction and preeclampsia. *American Journal of Obstetrics and Gynecology* 2006;195:40–9.
46. Nohr EA, Frydenberg M, Henriksen TB, Olsen J. Does low participation in cohort studies induce bias? *Epidemiology* 2006;17(4):413–8. [PubMed: 16755269]
47. Stewart A, Jackson R, Ford M, Beaglehole R. Underestimation of relative weight by use of self-reported height and weight. *Am J Epidemiol* January 1;1987 125(1):122–6. [PubMed: 3788941]1987
48. Nohr E, Bech B, Vaeth M, Rasmussen K, Henriksen T, Olsen J. Obesity, gestational weight gain and preterm birth: a study within the Danish National Birth Cohort. *Paediatric and Perinatal Epidemiology* 2006;21(1):5–14. [PubMed: 17239174]



Table 1

Maternal characteristics, by SGA status

|   | Non-SGA (n=79,256) |      | Term SGA (n=1518) |      | Preterm SGA (n=234) |      |
|---|--------------------|------|-------------------|------|---------------------|------|
|   | n                  | %    | n                 | %    | n                   | %    |
| Maternal age*                                 |                    |      |                   |      |                     |      |
| <20   | 420                | 0.5  | 17                | 1.1  | 6                   | 2.6  |
| 20-25   | 10,832             | 13.7 | 243               | 16.0 | 37                  | 15.8 |
| 26-30   | 33,833             | 42.7 | 628               | 41.4 | 76                  | 32.5 |
| 31-35   | 26,084             | 32.9 | 460               | 30.3 | 79                  | 33.8 |
| >=36  | 8,093              | 10.2 | 170               | 11.2 | 36                  | 15.4 |
| Low socio-occupational status*                | 7,374              | 9.3  | 194               | 12.8 | 42                  | 18.0 |
| Smoking in pregnancy*                         |                    |      |                   |      |                     |      |
| None  | 59,072             | 74.5 | 848               | 55.9 | 129                 | 55.1 |
| Quit during pregnancy                         | 7,458              | 9.4  | 128               | 8.4  | 12                  | 5.1  |
| Smoking                                       | 12,732             | 16.1 | 542               | 35.7 | 93                  | 39.7 |
| Hypertension                                  |                    |      |                   |      |                     |      |
| Probable <sup>†</sup>                         | 2,013              | 2.5  | 64                | 4.2  | 6                   | 2.6  |
| Definite*                                     | 934                | 1.2  | 26                | 1.8  | 15                  | 6.6  |
| BMI   |                    |      |                   |      |                     |      |
| Underweight (<18.5)                           | 3,568              | 4.5  | 122               | 8.0  | 22                  | 9.4  |
| Normal (18.5-24.9)                            | 54,252             | 68.5 | 1,027             | 67.7 | 148                 | 63.3 |
| Overweight (25-29.9)                          | 15,238             | 19.2 | 255               | 16.8 | 43                  | 18.4 |
| Obese (>30)                                   | 6,204              | 7.8  | 114               | 7.5  | 21                  | 9.0  |
| Diabetes mellitus                             | 1,101              | 1.4  | 16                | 1.1  | 2                   | 0.8  |
| Spontaneous abortions < 12 weeks <sup>‡</sup> |                    |      |                   |      |                     |      |
| One   | 10,096             | 12.7 | 197               | 13.0 | 24                  | 10.3 |
| 2 or more                                     | 2898               | 3.7  | 63                | 4.2  | 19                  | 8.1  |
| One or more spontaneous abortions ≥ 12 weeks  | 2,835              | 3.6  | 48                | 3.2  | 11                  | 4.7  |
| Multiparous*                                  | 42,889             | 54.1 | 620               | 40.8 | 104                 | 44.4 |
| Time to pregnancy ≥ 12 months*                | 9,698              | 12.2 | 273               | 18.0 | 44                  | 18.8 |

\* Overall group differences, chi square <0.0001

<sup>†</sup> <0.001

<sup>‡</sup> <0.01

**Table 2**  
Risk (cumulative incidence) of SGA, term SGA and preterm SGA

|                               | SGA*<br>(n=1752) | Term SGA*<br>(n=1518) | Preterm SGA*<br>(n=234) | P†    |
|-------------------------------|------------------|-----------------------|-------------------------|-------|
| Maternal age                  |                  |                       |                         |       |
| <20                           | 1.2 (0.8-1.9)    | 1.0 (0.6-1.7)         | 2.8 (1.1-6.8)           | 0.05  |
| 20-25                         | 0.9 (0.8-1.1)    | 0.9 (0.8-1.0)         | 1.1 (0.7-1.7)           | 0.37  |
| 26-30                         | 1.0              | 1.0                   | 1.0                     |       |
| 31-35                         | 1.1 (1.0-1.3)    | 1.1 (1.0-1.2)         | 1.5 (1.1-2.1)           | 0.07  |
| ≥36                           | 1.3 (1.1-1.6)    | 1.2 (1.0-1.5)         | 2.0 (1.3-3.1)           | 0.04  |
| BMI                           |                  |                       |                         |       |
| Underweight (<18.5)           | 1.7 (1.4-2.0)    | 1.6 (1.3-1.9)         | 2.0 (1.2-3.1)           | 0.42  |
| Normal (18.5-24.9)            | 1.0              | 1.0                   | 1.0                     |       |
| Overweight (25-29.9)          | 0.9 (0.8-1.0)    | 0.9 (0.8-1.0)         | 1.0 (0.7-1.4)           | 0.48  |
| Obese (>30)                   | 0.9 (0.7-1.1)    | 0.9 (0.7-1.1)         | 1.1 (0.7-1.7)           | 0.48  |
| Hypertension                  |                  |                       |                         |       |
| Definite                      | 2.0 (1.5-2.8)    | 1.5 (1.0-2.2)         | 5.5 (3.2-9.4)           | <0.01 |
| Probable                      | 1.6 (1.3-2.1)    | 1.7 (1.3-2.1)         | 1.0 (0.5-2.4)           | 0.27  |
| Diabetes mellitus             | 0.7 (0.4-1.1)    | 0.7 (0.4-1.2)         | 0.5 (0.1-1.9)           | 0.57  |
| Multiparity                   | 0.5 (0.5-0.6)    | 0.5 (0.5-0.6)         | 0.6 (0.4-0.7)           | 0.89  |
| Smoking during pregnancy      | 2.9 (2.6-3.2)    | 2.9 (2.6-3.2)         | 2.7 (2.1-3.6)           | 0.71  |
| Sub-fertility characteristics |                  |                       |                         |       |
| Time to pregnancy ≥12 months  | 1.4 (1.2-1.5)    | 1.4 (1.2-1.6)         | 1.3 (1.0-1.9)           | 0.86  |
| 2 or more SABs ≤12 weeks‡     | 1.2 (1.0-1.5)    | 1.1 (0.8-1.4)         | 2.0 (1.3-3.3)           | 0.03  |
| 1 or more SAB >12 weeks‡      | 1.0 (0.7-1.3)    | 0.9 (0.7-1.2)         | 1.3 (0.7-2.3)           | 0.39  |

\* Adjusted simultaneously for each pre-existing factor, low socio-occupational status, and height

† Wald-like test that the effect of each pre-existing condition is the same for term SGA and preterm SGA

‡ Spontaneous abortions