Risk Factors and Adverse Pregnancy Outcomes in Small-for-Gestational-Age Births

BY

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ABSTRACT


The studies were undertaken to evaluate risk factors and outcomes in small-for-gestational-age (SGA) births, in cohort studies using the population-based Swedish Birth, Twin and Education Registers. A cohort study of pregnant women from Uppsala County evaluated the effect on birthweight by caffeine.

Maternal anthropometrics influence risks of SGA at all gestational ages. Smoking increases risks of moderately preterm and term SGA, while hypertensive disorders foremost increase the risk of preterm SGA. Monozygotic twin mothers have higher concordance rates in offspring birthweight-for-gestational length than dizygotic twin mothers, indicating genetic effects on fetal growth. Caffeine is not associated with a reduction in birthweight or birthweight-for-gestational age.

The increased risk of stillbirth in postterm pregnancies is explained by increased rates of SGA in postterm pregnancies. Births with malformations account for a large part of the SGA-related increased risk of infant death. SGA, as defined by an individualised birth-weight standard, is a better predictor of adverse pregnancy outcomes than the commonly used population-based birthweight standard.

Risk factors for SGA, as well as the prognosis for the SGA infant, vary with gestational age. However, the commonly used definition of SGA is probably a poor predictor of intrauterine growth retardation.

Key words: Pregnancy, birthweight, fetal growth retardation, small-for-gestational age, maternal anthropometrics, genetic, caffeine, stillbirth, postterm pregnancy, birthweight standard.

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'Hallo !' said Piglet, 'what are you doing ?'
'Hunting' said Pooh.
'Hunting what ?'
'Tracking something' said Winnie-the Pooh very mysteriously.
'Tracking what ?' said Piglet, coming closer.
'That’s just what I ask myself. I ask myself, What ?'
'What do you think you’ll answer ?'
'I shall have to wait until I catch up with it’ said Winnie-the-Pooh.
LIST OF PUBLICATIONS

The present work is based on the following papers, which will be referred to in the text by their Roman numerals.


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ACRONYMS AND DEFINITIONS

AGA: Appropriate-for-gestational-age.
BMI: Body Mass Index.
CI: Confidence interval.
FGR: Fetal growth retardation.
ICD: International Classification of Diseases.
IUGR: Intrauterine growth retardation.
LBW: Low Birth Weight (defined as a birthweight less than 2500 gram).
LGA: Large-for-gestational-age.
OR: Odds ratio.
PAR: Population Attributable Risk.
SGA: Small-for-gestational age.
Postterm birth: A birth at 42 completed gestational weeks or more.
Preterm birth: A birth at a gestational age less than 37 completed gestational weeks.

Infant death: A death occurring before the infant is one year old.
Neonatal death: A death occurring during the first 27 completed days of life.
Perinatal death: A stillbirth or a death occurring during the first six completed days of life.
Postneonatal death: A death occurring from the 28th completed day of life up to the age of one year.
Birth weight, a function of both gestational age and fetal growth, is the most important determinant of a newborn infant’s chances to survive and grow in health (WHO 1980, McCormick 1985). In 1917 the Finnish paediatrician Yllpö (Gooth 1980) concluded that infants with a birthweight less than 2500 grams were premature. In the 1940ies clinicians became aware that low birthweight did not necessarily signify an infant born preterm, but may also be caused by intrauterine growth retardation (IUGR) (McBurney 1946). In 1967 Lubchenko and Battaglia introduced the terms small-for-gestational age (SGA), appropriate-for-gestational age (AGA) and large-for-gestational age (LGA). Although risk factors for growth restriction and preterm birth are partly overlapping, few studies have tried to study risk factors for SGA by gestational age.

Fetal growth and birthweight are reported to be associated with both genetic and environmental factors, but the evidence for a genetic effect is inconclusive (Brooks 1995, Magnus 1985), and the mechanisms by which genes may influence birthweight are largely unknown. Among substances in common use, caffeine has repeatedly, but not consistently, been suggested as a cause of reduced birthweight or fetal growth (Shiono 1993).

The aetiology of SGA is very heterogeneous. Parental anthropometric variables influence fetal growth, but evidence suggests that SGA infants to short mothers are healthy, albeit small (de Jong 1997). Diagnostic measures identifying the healthy, small infant as opposed to the IUGR infant, are therefore important to establish. The prognosis of a SGA infant probably depends to a large extent on the gestational age, although this has not been explicitly studied. Preterm SGA births should have high infant mortality rates and fetal growth restriction also affects outcomes in post-term pregnancies (Divon 1998). The present studies aim to identify risk factors for SGA, SGA by gestational age, and perinatal outcomes in SGA births as well as indicating a new way of identifying the SGA infant at risk.
OBJECTIVES AND HYPOTHESES

The overall objectives of the study were to investigate risk factors for, and outcomes in, SGA births.

The specific hypotheses of the studies were:

- Risk factors for SGA birth vary by gestational age.
- Genetic effects on birthweight exist, and are mediated through effects on fetal growth rate rather than gestational length.
- Caffeine consumption in pregnancy is associated with reduced fetal growth.
- Adverse pregnancy outcomes in post-term births reflect an increased rate of SGA births in post-term births.
- A customised birthweight standard (i.e. a birthweight curve standardised for maternal height, weight, parity and ethnicity) can improve the identification of fetuses at risk of stillbirth, neonatal death and Apgar score below 4 at 5 minutes.
Factors affecting birthweight exert their influence through fetal growth or duration of the gestation. *Gestational length* is the most important determinant of birthweight. The present study is concerned primarily with factors affecting fetal growth, but risk factors for fetal growth restriction and preterm birth partly overlap.

**Genetic and constitutional factors.**

*Fetal gender* influences intrauterine growth rate and consequently birthweight. Male infants have higher birthweight than females at the same gestational length, and at term this difference is approximately 100 gram (Marsál 1996). The gender difference in fetal growth becomes apparent in the third trimester of gestation, and recent studies have implied that it is partly mediated by an increased growth of the male fetus in the last two gestational weeks (de Jong 1998). Infants with *chromosomal aberrations* are more often SGA compared with infants with a normal karyotype (Snijders 1993). Globally, birthweights vary between different populations, probably reflecting genetic (Magnus 1984) as well as socio-economic effects (Kleinman 1987, Wilcox 1993, Wang 1995, Wen 1995). A normal range of fetal size, differing between ethnic groups, seems to exist, as well as small innate differences in gestational length (Migone 1991, Spencer 1995, Wilcox 1993).

Both *maternal and paternal size* at birth and as adults affect the infant’s birthweight (Langhoff-Roos 1987, Emanuel 1992, Brooks 1995, Klebanoff 1998). Whether the maternal effects are mediated through genes reproduced in the fetus or through a maternal "constraining mechanism" is a matter of controversy (Ounsted 1986), but *maternal anthropometrics* clearly affect size at birth. Short mothers have higher rates of SGA infants than tall mothers. Low *Body Mass Index* (BMI) and *low weight gain in pregnancy* are also identified as risk factors for SGA birth.

**Demographic factors.**

*Maternal age* is, in most studies, associated with a variation in rates of SGA, with the highest rates found in teenage and older mothers (Cnattingius 1992). Maternal age is, however, closely linked to parity, which also affects the risk of SGA birth. Maternal age and parity also interact with ethnic origin, and lifestyle differences, with higher
risks for nulliparas and grand multiparas. *Socio-economic status* also influences fetal growth, partly through differences in lifestyle habits such as smoking.

**Toxic exposure.**

*Smoking* is causally associated with intrauterine growth restriction, and constitutes an important preventable cause of IUGR in the western world (Kramer 1987). Nicotine in the form of tobacco chewing has also been associated with reduction in birthweights (Kramer 1987). Other toxic agents reported to be associated with IUGR are *alcohol* and *caffeine* (Brooke 1989) and *heroin* (Hulse 1997). The results from studies on caffeine exposure and birthweights are conflicting (Martin 1987, Brooke 1989, Peacock 1991, Olsen 1991, Larroque 1993, Mills 1993, Shu 1995, Cook 1996), but, as caffeine is a prevalent exposure, this association is of potential public health interest. *Viral infections* during pregnancy, such as cytomegalovirus, enterovirus, rubella, and varicella, have also been associated with IUGR (Stagno 1995, Van den Veyver 1998, Gershon 1995).

**Obstetric factors, nutritional status and maternal morbidity.**

*Previous SGA birth* is an established risk factor for SGA; some women are “repeaters” of SGA birth. This may reflect an innate tendency to have small babies, or a persistence of other risk factors, such as smoking in subsequent gestations (Bakketeig 1986). *Maternal diet* in early pregnancy is also known to affect fetal growth (Stein 1975, Godfrey 1996). *Low pregnancy weight gain* is a well-known risk factor for SGA birth (Kramer 1987).

Severe *anaemia* has been reported to affect fetal growth, other studies, however, demonstrate higher birthweights in women with a low hemoglobin concentration in pregnancy (Steer 1995). Pregnancy complications such as hypertensive diseases also affect fetal growth. *Maternal chronic diseases,* such as severe *pre-gestational diabetes,* *essential hypertension,* renal failure and coronary disease affect fetal growth (Carlsson 1988, Davison 1991, Haddad 1999).
METHODS

DATA SOURCES.

*The Swedish Medical Birth Register.*
The Swedish Medical Birth Register, held by the National Board of Health and Welfare, contains data on more than 99% of all births in Sweden (Cnattingius 1990). The register is compiled from standardised forms used at all antenatal clinics, delivery units and examinations of newborn infants throughout Sweden. Starting with the first antenatal visit, information is prospectively collected, including demographic data, reproductive history, and complications during pregnancy, delivery and the neonatal period. Copies of the standardised individual records are forwarded to the Birth Register. All births and deaths are validated every year against the Swedish Register of Total Population. Information about infant mortality is obtained through individual record-linkage between the Birth and Cause of Death Registers. The mother’s country of birth is derived by linking the Birth Register to the Civil Registration, held by Statistics, Sweden.

*The Cause of Death Register.*
This register is kept by the National Board of Health and Welfare, and records information on all diseased persons registered in the country at the time of death. The cause of death is generally determined from the medical death certificates, completed and filed by the attending physician or coroner. All causes of death are coded according to ICD classifications.

*The Education Register.*
This Register was established by Statistics, Sweden in 1985. It includes information on the highest formal level of education attained for each individual, from elementary to post-graduate level. It is updated annually.

*The Swedish Twin Register.*
The Swedish Twin Register, kept by the Karolinska Institutet, includes data on all twins born in Sweden from 1886 through 1958. Zygosity is determined on the basis of childhood resemblance, and has been validated by serological analyses (Cederlöf 1961,
Medlund 1976), and by DNA analyses (Svedberg 2000). In twin studies it is possible to quantify genetic effects, shared environmental effects, and non-shared environmental influences on the proneness to develop a certain trait or condition.

The Uppsala county cohort.
The data in paper III is derived from a prospective cohort study of 953 women invited to participate (from January 1996 through September 1998) as controls in a case-control study of early fetal loss in Uppsala county, Sweden. The women were interviewed, through in-person interviews, twice during pregnancy, using structured questionnaires. The interviews took place between the 6th and the 12th, and the 32nd to 34th completed week of gestation according to the last menstrual period. All participants were asked to report all known sources of caffeine intake on a week by week basis at the first interview and on a two week basis at a second interview in the third trimester. Plasma cotinine levels were also ascertained. Smoking, alcohol intake, and pregnancy related symptoms such as nausea, vomiting, fatigue, and aversion to specific food or beverage items were also reported, as well as other potential confounders. Delivery files were retrieved to find data on diseases before or during pregnancy, birthweight, gestational length, infant sex, and other pregnancy outcomes.

DESIGN OF THE STUDIES.

Paper I.
A cohort study of risk factors for SGA by gestational age, and infant mortality rates by gestational age among SGA and appropriate-for-gestational age (AGA) infants.

Information on live single births to primiparas in the Swedish Birth Register 1992-93, was linked to information from the Education Register. Details about subjects, outcome measures and covariates are given in Table 1.

Paper II.
A cohort study of genetic effects on birthweight, gestational length and birthweight for gestational length.
We used twin mothers of known zygosity, born before 1959, who both were found in the Medical Birth Register (i.e. had given birth from 1973-1993). Details about subjects and outcome measures are presented in Table 1.

**Paper III.**
A cohort study of the effect of caffeine on birthweight and fetal growth.

In all 953 mothers who were recruited at 6 to 12 completed gestational weeks from 1996 to 1998 in Uppsala County, Sweden. Information on caffeine consumption in pregnancy, smoking status, plasma cotinine levels, pregnancy symptoms and other potential confounders were collected at two interviews during pregnancy (at 6 to 12 weeks and 32 to 34 weeks, respectively). In all 881 women with single births were interviewed twice during pregnancy. Outcome measures and covariates are listed in Table 1.

**Paper IV.**
A cohort study aiming to identify the role of SGA in post-term pregnancy, with special reference to risk of stillbirth.

We used information from the Swedish Birth Register 1991-95 on term and post-term singleton births (n=510,029). Births were stratified as SGA and AGA. Outcome measures are described in Table 1.

**Paper V.**
A comparison of two different birthweight standards, and their respective association with adverse pregnancy outcomes.

Information from the Swedish Birth Register 1992-95 is used. Births were identified as SGA by conventional population based standards, or by an individualised, "customised" standard, and the risk of the outcome measures was assessed. Outcome measures are listed in Table 1.
Table 1. Overview of the papers.

<table>
<thead>
<tr>
<th>Paper</th>
<th>Subjects</th>
<th>Outcome measures</th>
<th>Covariates/ independent variables</th>
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<td>IV</td>
<td>510,029 term and post-term SGA and AGA singleton births 1991-95.</td>
<td>Odds ratios for stillbirth, neonatal death, Apgar score under 4 at 5 minutes, meconium aspiration, neonatal convulsions.</td>
<td>Term and post-term SGA and AGA births.</td>
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<td>V</td>
<td>326,377 singleton, non-anomalous births in Sweden 1992-95.</td>
<td>Risk of stillbirth, neonatal death and Apgar score under 4 at 5 minutes. Population attributable risk of stillbirth.</td>
<td>SGA, as defined by two different birthweight standards.</td>
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DEPENDENT VARIABLES.

Estimation of gestational length.
Several studies have found ultrasonography to be more accurate than last menstrual period in determining gestational age even in women with regular periods (Campbell 1985, Waldenström 1990, Kieler 1995, Mongelli 1996). At Swedish antenatal clinics, pregnant women are offered a second trimester ultrasound examination. In 1996 the Swedish Council on Technology Assessment in Health Care estimated that 96.6 % of pregnant women had availed themselves of this opportunity. Fifty-eight out of 59 units performing routine scans use only the data from the scan to estimate the gestational age. A questionnaire to all obstetric ultrasound units administered in 1996 concerning the timing of the routine ultrasound examination revealed that most units scan at 16-20 weeks gestational age. The examination is performed by a specially trained midwife or a physician (SBU report no. 139.1998).

The Swedish Medical Birth Register includes since the start (1973) date of delivery, as estimated by the last menstrual period. Since 1991, the Birth Register also includes information about estimated date of delivery by ultrasound examination. In study II, where most births took place before the 1990ies, information about gestational age was primarily based on the last menstrual period, but ultrasound examinations became increasingly common during the study period. In studies I, IV and V, births took place in the 1990’s, and information about gestational age was primarily based on ultrasound examinations. If information about estimated date of delivery by ultrasound was unavailable, the last menstrual period was used. In study III (the clinical cohort study), information about gestational age was based on a second trimester ultrasound.

As time of fetal death was unknown in stillbirths, gestational age of the stillborn fetus is based on the date of delivery in papers IV and V.

Gestational age
Gestational age was stratified into very preterm (≤ 32 completed weeks), moderately preterm (33 to 36 weeks) and term (≥ 37 to 41 weeks) (Paper I). In paper II, gestational age was stratified into preterm (≤ 36 weeks) and term (≥ 37 weeks). In Paper IV,
gestational age was stratified into term (37 to 41 weeks) and postterm births (≥ 42 weeks).

**Birthweight**

Low birthweight was defined as a birthweight <2,500 grams (paper II).

**Birthweight for gestational age**

In papers I, II, and IV, SGA was defined as a birthweight more than two standard deviations (SD) below the mean weight for the gestational age and gender, a weight above -2 SD but below +2 SD was denominated AGA, and a weight above +2SD is denominated LGA. This was done using a national standard for fetal weight by gestational age determined by consecutive ultrasound examinations (Marsál 1996)). In the clinical cohort study (paper III) birthweight ratio was defined as a deviation from the expected gestation- and gender-standardised birthweight using the same standard. In paper V, birthweight centiles were calculated according to two methods: a population standard and a customised standard. The population standard was adjusted for sex and gestational age, in which the birthweight of each delivery was given a centile based on the distribution of all births of the same sex at the same gestational age (in days). The customised standard is adjusted for sex, gestational age, as well as maternal height, weight, parity and ethnic group. Coefficients to adjust for these variables were derived from this population using stepwise multiple regression.

**Death**

Stillbirth included both antepartum and intrapartum deaths. A stillbirth was defined, in paper IV, as a dead fetus born at 37 completed weeks or later, in paper V as a dead fetus born at 28 completed gestational weeks or later. Neonatal death was defined as a death occurring during the first 27 completed days of life (paper I and V), and postneonatal death was defined as a death occurring from the 28 completed day of life up to the age of one year (paper I). Infant death was defined as a death occurring during the first year of life (paper IV).

**Infant Morbidity**

Low Apgar score at five minutes was classified as an Apgar score between 0 to 3 (papers IV and V). Infant diagnosis were classified according to the Swedish version of
the International Classification of Diseases, 9th revision (ICD-9). Neonatal convulsions (ICD-9 code 779A) and meconium aspiration (ICD-9 code 770B) were used as indicators of neonatal morbidity (paper IV). Congenital malformations were identified using the Birth and Cause of Death Registries (ICD-9 codes 740-759 as well as ICD-9 code 655 from the Birth Register ("known or suspected abnormality of the fetus affecting the care of the mother") (paper IV).

**Continuous variables**

When continuous variables were used (papers II and III), birthweight was measured in grams, gestational length in days and fetal growth in standard deviations from the gender specific birthweight curves.

In paper II, the continuous variables were controlled for parity and standardised, and values three standard deviations or more above or below the mean values were excluded. If a woman had more than one pregnancy, the mean value of all outcomes was used. Analyses were also performed on primiparous twin mothers only.

In paper III, the outcome variables were birthweight (in grams), gestational length (in completed days of gestation according to the second trimester scan) and birthweight ratio (defined as a deviation from the expected gestation- and gender-standardised birthweight according to Swedish birthweight standards.

An overview of the outcomes used in each study is given in Table I.

**INDEPENDENT VARIABLES.**

**Maternal age**

In paper I and V, maternal age was defined as completed years at time of delivery. In paper III maternal age was defined as completed years when the women was included in the study.

**Maternal height and weight**

Information about maternal height is based on maternal recall at the first visit to antenatal care and is expressed in centimetres (papers I, III and V).

Information about maternal weight was based on routinely measured weight at registration to antenatal care in papers I and V, while self-reported pre-pregnancy
weight was used in paper III. Body mass index (BMI) was defined as the weight in kilograms divided by height in meters to the second power (papers I, III and V).

**Smoking**

Smoking was categorised into non-smoking (i.e. non-daily smoking), moderate smoking (1-9 cigarettes per day) and heavy smoking (10 cigarettes or more per day) at registration to antenatal care in papers I and V. In paper III plasma cotinine levels in the first and third trimester were used as a proxy for smoking. Smokers were defined as subjects who had a cotinine level above 15 ng/ml (Peacock 1998) (paper III).

**Education.**

The mother’s formal education was defined as number of completed years at school, as recorded in the Education Registry January 1st, 1995 (papers I and V). In paper III formal education in years was assessed by interview data.

**Country of birth.**

In papers I and V, information about the mother’s country of birth was derived from the Birth Registry. In paper I, country of birth was defined as birth in a Nordic country (Sweden, Denmark, Norway Finland or Iceland) or outside the Nordic countries. In paper V, the mother’s ethnic group was defined according to country of birth, and included 26 countries for which sufficient numbers were available to derive adjustment coefficients. In paper III, the country of birth was ascertained through interview data.

**Diseases during pregnancy or delivery**

In paper I, diseases during pregnancy or delivery were classified according to the Swedish version of the International Classification of Diseases, ninth revision (ICD-9). Hypertensive diseases include essential hypertension (ICD-9 code 642 A), gestational hypertension (ICD-9 codes 642D and 642X) and preeclampsia (ICD-9 codes 642E and 642F). In paper III, ICD-10 codes were used: essential hypertension (O10), gestational hypertension (O13.9), preeclampsia (O14), pregestational diabetes (E10-14), and gestational diabetes (O24). Anaemia was defined as a hemoglobin concentration under 110 gram/litre at any time during pregnancy (paper III) (CDC criteria 1989).
Caffeine
Caffeine sources included coffee, tea, cocoa, chocolate, soft drinks and caffeine containing medications. Weekly caffeine intake was estimated through interviews, and calculated as a mean daily intake expressed in mg/day for each trimester, and as a total caffeine/day in pregnancy (paper III).

Parity
was defined as number of births before the index pregnancy (papers III and V).

Previous low birthweight infant
was defined as a previous birth of an infant with a birthweight of less than 2,500 grams (paper III).

Working hours per week
was stratified into 35 hours of work per week or less, and more than 35 hours per week (paper III).

Pregnancy symptoms
Nausea, vomiting and fatigue was determined by a severity score (paper III).
Pregnancy symptom scores were determined for each week or each two weeks of pregnancy by assigning a score for nausea (0 = never; 1 = sometimes; 2 = daily but not all day; 3 = daily, all day), vomiting (0 = never; 1 = sometimes but not daily; 2 = daily), and fatigue (0 = no; 1 = yes, but unchanged sleeping habits; 2 = yes, slightly changed sleeping habits; 3 = yes, pronounced change in sleeping habits). The weekly score for each symptom was summed from the estimated time of conception to the most recent completed week of gestation, and then divided by the number of weeks to arrive at an average score for each symptom. Change in eating habits in pregnancy was categorised as presence or absence of change in dietary patterns during pregnancy (paper III).

The customised birthweight standard
In the customised birthweight standard the birthweight centile is adjusted for sex and gestational age as well as maternal height, weight, parity and ethnic group. Coefficients to adjust for these variables are derived from the population, using stepwise multiple regression (Gardosi 1992, Gardosi 1995). The coefficients are used to calculate the
optimal weight achievable at the end of a standard length of pregnancy (280 days). A proportionality formula is then used to calculate the corresponding optimal weight, which should have been achieved at the length of gestation reached in each pregnancy. This optimal, gestation adjusted weight is compared with the actual weight, and the deviation is expressed as an individually adjusted or ‘customised’ centile.

ANALYSES.

In paper I, logistic regression analyses were performed to calculate adjusted odds ratios for the independent variables, using 95% confidence limits. Initially all maternal risk factors were included in the analyses, but the final model only included variables that significantly contributed to the model.

In paper II standard quantitative methods were used for the estimates of the relative contributions of genetic and environmental factors. For the dichotomised variables, probandwise concordance rates were calculated, representing the number of affected twins (giving birth to a low birthweight infant, an infant born preterm, or a small-for-gestational-age infant) in concordant pairs divided by the total number of affected twins with the same zygosity. The probandwise concordance rate represents the probability of a mother having a low birthweight infant, a preterm birth or a small-for-gestational-age infant, if her twin sister had the same pregnancy outcome. A higher rate in monozygotic than in dizygotic twins indicates that the variable is affected by genetic influences. However, this study design does not permit a separation of fetal and maternal genetic effects. Correlations were computed for each zygosity group. Higher correlations among monozygotic compared with dizygotic twins indicate a genetic component. For continuous variables correlations were calculated for each zygosity group.

By comparing covariance between twins of different zygosity, the proportion of variance of genetic effects (heritability) can be estimated. Monozygotic twins share identical genotypes, whereas dizygotic twins share on average 50% of their segregating genes. Genetic effects are indicated if monozygotic twins are more similar than dizygotic twins are.
In paper III mean daily caffeine intake was categorised as follows; 0-99 mg/day (referent), 100-299 mg/day, 300-499 mg/day and ≥ 500 mg/day. Univariate significance tests for the three outcome variables were performed by one-way analysis of variance. The initial multivariate model included caffeine intake and all variables judged to be influential in the univariate analyses, using the criteria p<0.1. Variables were thereafter eliminated by backwards selection until only significant variables (p<0.05) remained. Least-square means were used for multivariate adjustment. Covariates included in the statistical models are listed in Table 1.

In paper IV, logistic regression analyses were performed, including gestational age and birthweight as independent variables. Risks are expressed as odds ratios with 95% confidence intervals. Since the object of the study was to evaluate fetal growth restriction in relation to adverse events, we did not consider it appropriate to control for known risk factors for fetal growth restriction (e.g. smoking, maternal age, primiparity). Such risk factors are not truly confounders, but rather the first link in the causal chain between the risk factors and the outcome (Kiely 1991).

In paper V, outcomes were compared between SGA and non-SGA pregnancies, as defined according to birthweight curves using population centiles or customised centiles. Crude odds ratios and 95% confidence intervals were calculated for stillbirth, neonatal death, and Apgar score below 4 at 5 minutes. Odds ratios were calculated for combinations of non-SGA/SGA (defined as the lowest 10 %) by either standard, using non-SGA by both standards as the reference group. Odds ratio and population attributable risk (PAR) of stillbirth were calculated by different levels of SGA by either classification. Population attributable risk was defined as the fraction of the incidence of stillbirth that might be reduced when births with different levels of SGA were eliminated.
RESULTS

Paper I.
Among live single non-anomalous births to nulliparas, 3.8 % SGA births were recorded. SGA was more common in preterm than in term births. To investigate whether the risk of SGA related to maternal risk factors and hypertensive diseases was modified by gestational age, interaction terms between these covariates and preterm birth (≤36 weeks) were introduced in the logistic regression models. Significant interaction terms (p<0.05) were found between preterm birth and maternal age, height, smoking habits and hypertensive diseases. Analyses of risk factors for SGA were therefore stratified by gestational age. As hypertensive diseases are intermediate steps in the causal pathway linking maternal characteristics to SGA, risks of SGA in hypertensive diseases were presented using crude odds ratios. Hypertensive diseases were associated with increased risks of SGA regardless of gestational age, although essential hypertension and preeclampsia were foremost associated with substantially increased risks of preterm SGA.

Adjusted odds ratios were calculated for SGA by gestational age. Increasing maternal age and decreasing maternal stature were associated with SGA at all gestational ages. Lean mothers had slightly increased risks of term SGA and mothers with short education had slightly increased risks of preterm SGA. Smoking was associated with dose-dependent increased risks of moderately preterm and term SGA.

Infant mortality rates were higher among SGA infants compared with non-SGA infants. Infant mortality was above all influenced by gestational age, but within each gestational age strata, SGA infants had higher mortality rates than AGA infants.

Paper II.
Among monozygotic twins of whom at least one twin in a pair had a low birthweight infant (n=90), 18 also had a sister with a low birthweight infant (probandwise concordance rate=0.20). Probandwise concordance rate among 114 dizygotic twins, calculated in the similar manner, was 0.07. The correlations of liability for low birthweight were 0.42 and 0.09 for monozygotic and dizygotic pairs, respectively. The
concordance rates and correlations for preterm birth and small-for-gestational-age were also higher among monozygotic compared with dizygotic twins.

Correlations for mono- and dizygotic twins using continuous variables were calculated in a similar manner. Correlations for birthweight, gestational length and fetal growth rate were analysed separately for each zygosity group and were higher in offspring of monozygotic twins compared with dizygotic twins.

The quantitative genetic analyses presented give the estimates of heritability for low birthweight at 37%. For preterm birth, heritability was estimated at 36%. Fit-of-model for preterm birth was adequate, whereas the models using gestational length as a continuous variable only had a modest fit. For small-for-gestational-age, the heritability estimate was 34%. When birthweight, preterm birth and small-for-gestational-age were analysed as a continuous variable, estimates did not change noticeably.

**Paper III**

In univariate analyses, neither total caffeine (expressed as mean daily consumption in mg) nor caffeine stratified by trimester had a significant effect on birthweight, gestational length or birthweight ratio. Smoking, measured as cotinine levels in the third trimester, affected birthweight and birthweight ratio. Maternal age, height, BMI, country of birth and education were also significantly associated with reduced birthweight and/or gestational length. The presence of diabetes or hypertensive diseases in pregnancy also significantly influenced birthweight and gestational length. In multivariate analyses, mean caffeine consumption during pregnancy was used. Total caffeine consumption per day was not associated with changes in birthweight or birthweight ratio, whereas cotinine levels in the third trimester, maternal stature, maternal BMI and parity all affected birthweight and birthweight ratio.

We found no interaction between caffeine and smoking with regard to birthweight or birthweight ratio.
Paper IV.
To evaluate the contribution of congenital malformations to stillbirth, infant mortality and neonatal morbidity, odds ratios were calculated both including and excluding births with malformation diagnoses, using term AGA births as the reference group. SGA births had substantially elevated risks of stillbirth, and these estimates remained essentially unchanged after excluding births with malformations. Term SGA births faced a more than seven-fold increase in risk of infant death, which was substantially reduced after excluding malformed infants. In post-term SGA births, a five-fold increased risk of infant death was eliminated after excluding malformed infants from the analyses. For post-term AGA births there was no significant increase in risk of infant death.

Risk of convulsions were increased in SGA births irrespective of gestational length, as well as in post-term AGA infants, but estimates remained in the same range when malformed infants were excluded from the analyses. For meconium aspiration, a similar pattern was seen, but post-term AGA births had the highest increase in risk, and the risk was not significantly increased for post-term SGA births. Term SGA infants had a fourfold increase in risk of Apgar score under 4 at 5 minutes, which was reduced after excluding malformed infants from the analyses. Post-term infants faced an increase in risk of Apgar score under 4, which was unaltered after excluding malformed infants.

We estimated the population-attributable risk of stillbirth and infant mortality as a consequence of SGA. The overall population-attributable risk of stillbirth and infant mortality due to SGA was 14.2 % and 12.3 %, respectively. In term births, corresponding risks amounted to 13.2 % and 12.3 %, and in post-term births to 22.0 % and 11.3 %.

Paper V.
Teenage mothers and primiparas had increased risks of SGA by population standards, but no increase in risk by customised standards. Mothers who were 30 years or more had no increased risk of SGA by the population standard, but an increased risk of SGA by the customised standard. Mothers born outside the Nordic countries faced a 60% increase in risk of an SGA birth by the population standard, but this risk was eliminated.
when customised standards were used. Risk of SGA by population standards decreased with increasing BMI, whereas women with BMI of 30 or more had a 50% increase in risk of SGA by customised standards. A reduced risk of population based SGA was seen with increasing maternal height, but when customised standards were used short women (below 155 cm) had a significantly reduced risk of SGA. The smoking-related risk of SGA was slightly more pronounced when customised assessment was used. Births classified as SGA by the customised standard had a considerably elevated risk of stillbirth (five- to six-fold), regardless of whether they were SGA by the population standard. In contrast, births, which were classified as SGA only by the population standard, did not show an increased risk of stillbirth. Risks of neonatal death or Apgar score under 4 at 5 minutes showed a similar pattern.
DISCUSSION

Risk factors for SGA vary by gestational age, and SGA infants have higher death rates than AGA infants at all gestational ages. In post-term pregnancy there is an increased rate of SGA births, which appears to explain the increased risk of stillbirth observed among post-term pregnancies. Genetic factors appear to influence fetal growth as well as gestational length. We find no evidence that caffeine consumption during pregnancy influences fetal growth. Maternal anthropometrics influence risk of SGA birth, as commonly defined by population-based birthweight standards. Compared with SGA defined by population-based birthweight standards, SGA defined by birthweight curves standardised for maternal height, weight, parity and ethnicity ("customised" birthweight standards) increases the strength of the associations between SGA birth and adverse outcomes, such as stillbirth.

General considerations.

Papers I, II, IV and V are based on register data covering the Swedish population. We have, in studies I and II, taken advantage of the possibility to link information between registers, and thereby obtained large sample sizes and almost complete national coverage. Information on covariates are collected prospectively and independent of study outcomes.

Three cohort studies (papers I, IV and V) based on the Medical Birth Register are large and have the power to investigate rare outcomes. In paper II the sample size is smaller, and in paper III, the Uppsala county cohort, the study size is also limited. As a result, estimates in these studies to some extent suffer from low precision. In paper V, we were, due to missing information about covariates, forced to exclude 22.5 % of all births, where we could not calculate a customised birthweight centile. In the Medical Birth Register data on pregnancy outcomes (such as stillbirth, birthweight, gestational age and Apgar score) and most covariates (such as maternal sociodemographic and anthropometric characteristics) are of a high quality (Cnattingius 1990). Maternal and infant diagnoses are based on ICD-codes, and the information is somewhat less reliable. Data in the Cause of Death Register is also of a high quality, with rare instances of missing cases and few misclassifications of cause of
death (National Board of Health and Welfare, 1998). In the Education Register information on highest attained level of education is correctly recorded for 82% of women (Cnattingius 1997). In The Twin Register, previous validations have concluded that zygosity is correctly determined for 99% of monozygotic and 92% of dizygotic twins (Medlund 1976).

**Risk factors for SGA.**

Though the aetiology of SGA is complex, three distinct subgroups can be discerned: the constitutionally small, healthy infant, the infant with chromosomal or other dysfunctions that exist from the onset of pregnancy, and the growth restricted, non-malformed infant. While risk factors for chromosomal and other inborn dysfunctions naturally exist, they are beyond the scope of the present study. Some previously described risk factors for SGA are merely risk factors for constitutional, healthy smallness, whereas others are risk factors for IUGR.

As in previous studies (Cnattingius 1992), we found high maternal age (thirty years or more) to be associated with increased risk of SGA, both in preterm and term births (paper I). We speculate that this risk reflects an association with IUGR, as an age-related increase in risk of constitutional smallness seems unlikely. Maternal age is also related to risk of stillbirth (Nybo Andersen 2000), a risk which cannot be explained by increased risks of SGA, as defined by conventional birthweight standards (Raymond 1994). However, it remains to be determined whether the age-related effect on stillbirth can be explained by SGA as defined by a customised standard. In paper V we found that high maternal age increases the risk of customised SGA, and customised SGA increases the risk of stillbirth. Therefore, possibly part of the maternal age related increase in risk of stillbirth could be explained by customised SGA.

Maternal anthropometrics, such as height and BMI affect birthweight. Whether the association of maternal height and SGA (paper I) is an association with constitutional smallness or with IUGR is unclear, but data supporting a relation between maternal height and perinatal mortality indicate to some extent an association with IUGR. Cnattingius et al (Cnattingius 1998) found that the risk of stillbirth was lower among SGA fetuses in short compared to tall mothers, but that SGA was, irrespective of
maternal stature, associated with an increased risk of stillbirth. Maternal BMI affects risk of term SGA with modest increases in risks for lean mothers.

Caffeine is a prevalent exposure, and an association with reduced birthweight should therefore be of public health interest. Though limited in size, our study (paper III) should have sufficient power to detect a substantial effect of caffeine on fetal growth. We therefore conclude that caffeine does not substantially influence fetal growth, but we may have been unable to detect modest effects of caffeine on birthweight and birthweight ratio. Moreover, since we used continuous outcomes, the results do not allow us to conclude that caffeine exposure is unrelated to low birth weight or SGA births.

Hypertensive diseases in pregnancy, notably essential hypertension and preeclampsia, substantially influence fetal growth. As the risk of developing pregnancy-induced hypertensive diseases is influenced by factors such as maternal age, BMI, smoking status and ethnicity, pregnancy-induced hypertensive diseases may be considered as intermediate steps in the causal pathway linking maternal characteristics to SGA. We therefore found it appropriate to exclude hypertensive diseases from the multivariate analysis of maternal characteristics and SGA (paper I).

Genetic factors influence not only birthweight and fetal growth, but also gestational length (paper II). The mediation of genetic effects on birthweight and gestational length is still largely unknown. Genes that influence these outcomes can operate through many channels, such as anthropometrics, lifestyle factors, and susceptibility to disease during pregnancy (Dunger 1998). The maternal genetic influence on fetal growth can therefore vary between populations. Presumably, in a population with a high degree of maternal morbidity genetic effects will be of less importance, whereas, in a healthier population, genetic influence on birthweight will be relatively more important. Gene expression can furthermore be modified by environmental factors. For example, Van Baal et al showed that maternal smoking modifies genetic effect of birthweight. (Van Baal 1998).
Risk factors for SGA by gestational age.

The relationship between SGA and preterm birth is complex: risk factors for SGA and preterm birth partly overlap, and SGA, as defined by standards aiming to reflect fetal growth, is more common in preterm than in term births. Preterm birth is associated with increased risk of infant death, and short- and long-term morbidity. Analysis of risk factors for SGA by gestational age can therefore add insights into this complex problem.

We found that hypertensive diseases in pregnancy are associated with SGA at all gestational ages, but risk estimates are decidedly affected by gestational age (paper I). There is a strong association between essential hypertension and preeclampsia and preterm SGA, particularly very preterm SGA. From a clinical point of view these risk factors are probably associated with pathological conditions in pregnancies where SGA serves as an approximation of the dynamic concept of IUGR.

Whether short maternal stature has an independent increase in risk of IUGR, or just an increased risk of the statistically defined SGA is unclear. The overall risk of SGA increases with decreasing maternal height (paper I). This inverse relationship probably to some extent reflects genetic factors (paper II) (i.e. a small mother giving birth to a small but healthy infant), and could explain the increased risk of term SGA related to short stature. Short mothers also had an increased risk of preterm SGA births, which probably reflects that maternal stature influences fetal growth during all pregnancy. Some previous studies have found increased risk of perinatal death in short compared to tall women, whereas others have found no such association (Golding 1991). A related question is whether ethnicity is associated with risk of IUGR. We found increased risks of term SGA for mothers born in non-Nordic countries compared to mothers born in Nordic countries (paper I), but customised standards displayed lower risk of SGA for non-Nordic mothers compared to Nordic mothers (paper V). We interpret this as due to the lower prevalence of smoking among non-Nordic mothers, and this illustrates that ethnicity is not only associated with maternal size, but also with lifestyle practises. The prevalence of pathological conditions in pregnancy, such as pregnancy-induced hypertensive diseases and gestational diabetes also varies with ethnicity (Ros 1998).
Smoking in pregnancy is a risk factor for SGA birth and we found dose-response relationship between smoking and moderately preterm and term SGA birth, but no association with very preterm SGA birth (paper I). Reassuringly, population-based and customised birthweight standards show similar risk estimates for SGA in smokers (paper V).

**The prognosis of the SGA infant**

As expected, the prognosis of an SGA infant was severely dependant on gestational age (paper I), but SGA infants had higher neonatal and post-neonatal mortality rates than AGA infants at all gestational ages. SGA influenced death rates relatively less in very preterm births than in moderately preterm and term births. The relatively stronger impact of SGA in moderately compared to very preterm births is probably due to lower mortality rates attributable to prematurity problems.

SGA also substantially influenced stillbirth rates in term and post-term pregnancies (paper IV). Compared to term AGA births, we found that SGA births were associated with an eightfold increase in risk of stillbirth at term, and a tenfold increase in risk in post-term pregnancies, with population attributable risks of stillbirth of 13 % and 22 %, respectively. As risk of stillbirth was not increased in postterm AGA pregnancies, we conclude that the increase in risk of stillbirth in post-term pregnancies is merely a reflection of an increased rate of SGA pregnancies. A strong association of infant death with SGA birth at term and post-term was also seen, but risks were materially reduced when births with congenital malformations were excluded. For the AGA post-term infant we found no increase in infant mortality, but increased risks of neonatal morbidity.

Estimates of stillbirth by gestational age should preferably be calculated using ongoing pregnancies as denominator, rather than stillbirth calculated as a rate per all births at that specific gestational age (Hilder 1998). The latter method only estimates what proportion of births are stillborn, which is not an estimate of fetuses at risk. However, the former approach was not possible to use when we calculated risk of stillbirth among term and post-term SGA and AGA births, since this would force us to assume
that infants who were born SGA also were SGA in utero several weeks earlier. Therefore we preferred to present rates of stillbirth as mortality rates (number of stillbirth per all births).

**Maternal anthropometrics and SGA birth**

As IUGR is difficult to ascertain antenatally, SGA often serves as a proxy for IUGR. As previously pointed out, SGA is a heterogenic concept, including not only IUGR, but also chromosomal aberrations as well as healthy, genetically small individuals. The commonly used, population-based birthweight standards cannot differentiate between these subgroups, and use SGA as a statistical definition of the dynamic concept of IUGR. We hypothesise that the customised birthweight standard approximates SGA to IUGR: applying a customised birthweight standard, we can better discriminate between risk factors associated with IUGR (e.g. smoking) from mere risk factors for SGA (e.g. country of birth).

**Birthweight standards.**

A birthweight for gestational age standard based on the distribution of birthweight at different gestational ages may be relevant in a clinical context for term births, but is considerably less appropriate in both the preterm and the postterm period. Preterm birth is, per se, a non-normal event, and the distribution of birthweights in preterm births reflect pathological conditions. The commonly used birthweight-for-gestational-age standard therefore produces lower birthweights in the preterm period compared to ultrasound-based estimated fetal weights of normal pregnancies in the corresponding weeks. "Hybrid" growth curves based on estimated fetal weights in the preterm period and birthweights in term births have been suggested (Bernstein 1996). This, however, does not solve the problems with genetic variations in birth size at term, nor the problems associated with birthweight standards in the postterm period. We have shown, in our data based on ultrasound estimated fetal weights, an increased prevalence of SGA births postterm, with corresponding increased risks of adverse outcomes such as stillbirth. A recently published birthweight standard based on gestational age estimated by last menstrual period (Skjærven 2000) shows decreasing mean birthweights in gestational weeks 43 and 44, which is biologically unlikely. If a
birthweight standard is to be useful in a clinical context, it should indicate the expected fetal growth in a normal pregnancy, rather than simply reflect mean birthweight by gestational age.

**Implications for the future.**

Further investigations are needed in at least two fields.

We have concluded, in our study of caffeine consumption in pregnancy and birthweight, that caffeine, albeit its prevalence in the pregnant population, is not an important risk factor for reduced birthweight. A larger study might provide added information regarding a weak association between caffeine and reduced fetal growth, or whether caffeine increases the risk of SGA births.

Furthermore, the field of antenatal detection of reduced fetal growth needs to be investigated. We have shown that customising birthweight standards improves prediction of adverse outcomes in SGA births, but this is a diagnosis at birth. In order to be clinically useful, the customisation principle must be used antenatally. Customisation of symfyseal-fundal heights is a possible method (Gardosi 1999). Further studies should ideally focus on antenatal detection of IUGR, by comparing the standard and customised symfyseal-fundal curves in a randomised trial.
CONCLUSIONS

• Risk factors for SGA vary with gestational age

• Compared with appropriately grown infants, SGA infants are at increased risk of death at all gestational ages.

• Genetic factors influence both birthweight and possibly also the length of the gestation.

• Caffeine consumption in pregnancy is not related to reduced fetal growth.

• The increased risk of stillbirth seen in postterm pregnancies is to a substantial degree explained by an increased rate of SGA births postterm.

• The appropriately grown postterm fetus has an increased risk of neonatal morbidity, but no increase in mortality.

• SGA defined by a customised standard improves identification of growth restricted infants at increased risk of primarily stillbirth.
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