Reasons for Increasing Trends in Large for Gestational Age Births

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OBJECTIVE: To describe the magnitude of change in the proportion of term and postterm (37 completed weeks or more) large for gestational age (LGA) infants between 1992–2001 in Sweden and to examine whether time trends in prevalence of LGA births can be explained by changes in maternal risk factors.

METHODS: Using the population-based Swedish Birth Register, we analyzed data from 1992 through 2001 on births of women who delivered live, singleton, term infants without malformations (N = 874,163). Unconditional logistic regression was used to model the odds of LGA birth.

RESULTS: Mean birth weight and proportions of LGA births and births 4,500 g or more rose during the period 1992 to 2001. An unadjusted analysis estimated that the risk of LGA birth increased by 23% over 10 years. However, the prevalence of overweight and obesity (body mass index of 25 or greater) increased from 25% to 36%, and the prevalence of smoking decreased from 23% to 11% during the same period. After adjusting trends in all covariates simultaneously, the association between risk of LGA birth and calendar year disappeared.

CONCLUSION: The increasing proportions of LGA births over time is explained by concurrent increases in maternal body mass index and decreases in maternal smoking. With the increasing prevalence of overweight among adolescents and young women, the prevalence of LGA infants and associated risks may increase over time. (Obstet Gynecol 2004;104:720-6. © 2004 by The American College of Obstetricians and Gynecologists.)

LEVEL OF EVIDENCE II-2

High birth weight (4,500 g or greater) is a risk factor for complications among both newborns and mothers.^{1,2}

Supported by the American-Scandinavian Foundation through a grant from the Thord-Gray Memorial Fund and through a grant from the Swedish Council for Working Life and Social Research (grant number 2001-2247). For infants, birth weight of more than 4,500 g has been associated with increased risks of infant mortality³ and traumatic injuries during delivery.⁴ Birth trauma associated with high birth weight specifically includes clavicle or humerus fractures and brachial or facial paralysis.⁵ High birth weight is also related to shoulder dystocia,^{1,6} although other factors may be involved. Adverse consequences may extend to later stages in life, including the later development of overweight^{7,8} and possibly breast cancer.⁹ For mothers, the delivery of a high birth weight infant is associated with genital tract injury,¹ prolonged labor,⁶ risk of postpartum bleeding,^{1,6} and an increased likelihood of cesarean delivery.^{3,6,10}

In Europe and North America there is an increasing proportion of infants born with a high birth weight.^{11,12} In the mid 1970s Swedish infants more than 4 kg accounted for 17% of births; however, by the beginning of the 1990s this had risen to 20%.¹¹ Research in North America and Europe has shown a similar pattern of increased numbers of large for gestational age (LGA) and high birth weight infants (more than 4,000 g), respectively¹³.¹⁴ Clearly, if these trends continue, obstetrical complications will rise concurrently.

Kramer et al¹² found that increasing maternal weight, gestational weight gain, gestational diabetes, and reduced smoking prevalence among pregnant women explained the temporal increase in proportion of LGA births between 1976 and 1996 in Canada. However, these findings require confirmation in other populations.

The Swedish Birth Registry allowed us to study time trends in LGA births in a large population-based setting. We restricted our sample to live singleton term births (37 weeks or more). The objectives of this study were first, to describe the magnitude of change in the proportion of LGA infants between 1992 and 2001 and second, to improve future possibilities of reversing an increasing trend of LGA births. We examined whether a change in rate of LGA births over time can be explained by a change in the panorama of maternal risk factors.

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SUBJECTS AND METHODS

The Swedish Birth Register is maintained by the National Board of Health and Welfare and includes more than 99% of all births in Sweden. The Birth Register includes information about 989,211 births from 1992 through 2001. We restricted the study population to women who delivered live, singleton infants without malformations born at 37 completed gestational weeks or later (N = 874,163).

Starting with the first antenatal visit, information is prospectively recorded and forwarded to the registry using standardized antenatal, obstetrical, and neonatal records. Data collected at the first prenatal visit include demographic and anthropometric information, previous reproductive history, and smoking habits. Subsequently, doctors and midwives collect data on maternal complications during pregnancy and delivery, gestational age, birth weight, and infant sex. The Birth Register includes information about the National Registration Numbers for both the mother and infant. The National Registration Number is a unique person-identifier and can link the registry to other population-based registries. The National Board of Health and Welfare validates births and deaths of infants each year, through cross-linkage with the Register of Total Population and Population Changes, held by Statistics Sweden. The Medical Birth Registry has recently been validated, and the quality of the variables included in the present investigation is high. Results from the validation study are available on the Web at www.sos.se/fulltext/112/2003-112-3/2003-112-3. pdf (retrieved August 5, 2004).

The maternal and pregnancy characteristics used as exposure variables were calendar year of birth, maternal age, parity, body mass index, maternal height, cohabitating with the infant's father or not, mother's country of birth, maternal smoking, gestational diabetes, preeclampsia, and gestational age. Maternal age was defined in completed years at delivery, using the following categories: 24 or less, 25-29, 30-34, or 35 or more years. Parity was defined as number of births including present birth, and was grouped into 1, 2, 3, 4, or 5 or more births. Information about body mass index (BMI) was based on measured weight (in kilograms) and self-reported height (in centimeters) at first prenatal visit. The BMI was calculated as weight in kilograms per height in meters², and women were categorized as lean (BMI 19.9 or more), normal (BMI 20.0 through 24.9), overweight (BMI 25.0 through 29.9), and obese (BMI 30.0 or more). Height measurements were categorized into the increments 159 or less, 160-164, 165-169, or 170 or more centimeters. Cohabitation was defined as whether the mother lived with the infant's father at registration to

antenatal care. Country of origin was defined as Nordic, including Denmark, Iceland, Norway, Sweden, or Finland, or non-Nordic. Maternal smoking was based on women's self-reports to the midwives at the first antenatal visit. Information on maternal smoking was recorded in a standardized manner, using 3 check boxes, by which women were grouped into non-, moderate (1-9 cigarettes per day), or heavy (at least 10 cigarettes per day) smokers. Preeclampsia and gestational diabetes were recorded at the time of discharge from the hospital. These disorders were defined according to the International Classification of Diseases, 9th and 10th Revisions (ICD-9, and ICD-10), from 1992-1996 and after 1996, respectively. Preeclampsia included ICD-9 codes 642E-642H, and ICD-10 codes O14 and O15. Gestational diabetes included ICD-9 code 648W and ICD-10 code O244. Term gestation was defined as 37-41 completed weeks, whereas a gestation of 42 weeks or more was considered postterm. In Sweden women are routinely offered early second trimester ultrasonography to estimate gestational age, and 95% percent of Swedish pregnant women accept this offer.¹⁵ Information on gestational age, birth weight, and sex was used to calculate birth weight for gestational age. An LGA birth was defined as a birth weight of more than 2 standard deviations above the mean birth weight for gestational age according to the Swedish reference curve for fetal growth.¹⁶ The ethics review board at Karolinska Institutet, Stockholm, Sweden approved this study.

We used unconditional logistic regression to estimate crude and adjusted odds ratios with 95% confidence intervals to examine the associations between maternal and pregnancy characteristics and risk of LGA. We commenced by estimating a model where calendar year of birth was the only explanatory variable. We modeled calendar year of birth divided by 10 as a metric variable to estimate the relative odds of LGA for a 10-year increase in year of birth. Building on this unadjusted model we estimated a series of multivariate models to examine how the estimated effect of birth year changed after adjusting for maternal and pregnancy characteristics. Because the prevalence of LGA birth is low, the estimated odds ratios can be interpreted as risk ratios (ratios of proportions).

Our model assumes that multiple births to the same mother are independent (conditional on covariates), which may not be strictly correct. We therefore estimated a marginal logistic regressions model using generalized estimating equations to account for the possible correlation between multiple births to the same mother. Such correlation, if present, would not bias the effect measure estimates but might result in underestimation of the standard errors. We found only negligible differ-



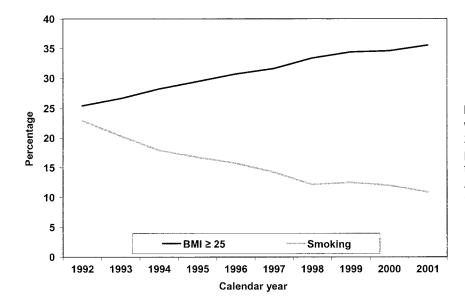


Fig. 1. Trends in prevalence of overweight and obesity (body mass index 25 or greater) and smoking (1 cigarette per day or more) in Sweden from 1992 to 2001. BMI, body mass index.

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ences in both the parameter and standard error estimates between the generalized estimating equations and the naive logistic regression models and do not present results based on generalized estimating equations models.

Information was not available on all covariates for all births; missing information was most prevalent for BMI (missing 17%), height (9%), cohabitation with child's father (7%), and smoking (5%). An appropriate analysis of incomplete data requires the assumption that the probability of missing data does not depend on the values of any of the missing, or unobserved, variables but might depend on values of observed variables. We restricted our analyses to the 861,608 births (of the 874,163 births eligible for the analysis) with complete information on maternal age, parity, country of birth, gestational diabetes, preeclampsia, gestational age, and calendar year of birth. We then assumed that the probability of missing data in the other covariates (BMI, height, cohabitation, and smoking) was a function of these known covariates.

We then estimated logistic regression models using the mean score method for incomplete data using Stata 8.2 software (StataCorp., College Station, TX).¹⁷ Mean score logistic regression weights the effect estimates of the incomplete covariates within strata specified by a subset of complete covariates that are both determinants of missing data in the incomplete covariates as well as associated with the incomplete covariates that are putative predictors for the outcome. We used multivariate logistic regression with missing data as the outcome to determine that missing data depended on year of birth, mother's country of birth, maternal age, and parity. Because of small numbers in some strata, parity could not be used as a stratification variable in the mean score modeling. Compared with analyses restricted to births with complete information on all births (n = 676,233) the estimated odds ratios and standard errors did not change substantially. We therefore chose to report estimates appropriately adjusted for incomplete data.

RESULTS

Mean birth weight, mean birth length, proportion of LGA births, and proportion of births with birth weight of 4,500 g or more all increased during the period 1992 to 2001. Mean birth weight increased from 3,596 g to 3,631 g, mean birth length increased from 50.5 cm to 50.7 cm, the proportion of LGA infants increased from 3.32% to 3.86%, and the proportion of infants weighing 4,500 g or more increased from 3.71% to 4.60% (data not shown).

Two factors related to birth weight that showed particularly strong trends during this period were an increase in prevalence of overweight and obese mothers (BMI 25 or more) (from 25.4% to 35.5%) and a decrease in the prevalence of daily smoking (from 22.9% to 10.9%) (Fig. 1). During the study period, the proportion of births to primiparous women rose from 40% to 44%, the proportion of older (35 years or older) mothers increased from 9.5% to 12.4%, and the proportion of non-Nordic-born mothers increased from 8% to 11%. There was no evidence of substantial temporal changes in the proportion of mothers not living with the infant's father, maternal height, preeclampsia, gestational diabetes, or length of gestation (data not shown).

Compared with women with normal BMI (20.0–24.9), overweight (BMI 25.0–29.9) and obese women (BMI 30.0 or more) had 2-fold and a more than 3-fold

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	No. births	Large for gestational age [†] (%)	Crude odds ratio (95% confidence interval)	Adjusted odds ratio [‡] (95% confidence interval)
.	NO. DITUIS	gestational age (10)		
Age (y)	1.00.074	0.5		
≤ 24	169,074	2.5	0.75 (0.72–0.78)	1.06 (1.01 - 1.10)
25-29	320,835	3.3	1.00	1.00
30-34	261,639	4.1	1.24(1.20-1.27)	1.02 (0.98 - 1.05)
≥ 35	122,301	4.7	$1.42 \ (1.37 - 1.46)$	$1.01 \ (0.97 - 1.05)$
Missing	314	4.1		
Parity	9.01 007	1.0	1.00	1.00
$\frac{1}{2}$	361,627	1.9	1.00	1.00
2 3	321,929	4.3	2.32 (2.25-2.39)	2.19(2.11-2.27)
	131,697	5.4	2.97 (2.87 - 3.07)	2.82(2.70-2.93)
$4 \ge 5$	$39,363 \\ 19,526$	6.1	3.34 (3.18 - 3.50)	3.16(2.98-3.36)
	19,520	$\begin{array}{c} 6.6 \\ 4.7 \end{array}$	3.65 (3.43-3.88)	3.23 (2.99-3.49)
Missing Roder more in dorr	21	4.7		
Body mass index ≤ 19.9	86,628	1.2	0.44(0.41, 0.47)	0.47 (0.44, 0.50)
		2.7	0.44 (0.41-0.47)	0.47 (0.44 - 0.50)
20-24.9 25-29.9	419,101	5.3	1.00	1.00
≥ 30	$162,043 \\ 58,191$	5.5 8.6	$\begin{array}{c} 1.98 \ (1.93-2.04) \\ 3.36 \ (3.25-3.48) \end{array}$	1.96 (1.90-2.02)
≥ 30 Missing	148,200	3.6	3.30 (3.23-3.48)	3.28 (3.16-3.41)
Height (cm)	146,200	5.0		
≤ 159	100,622	1.9	0.59 (0.57-0.62)	0.57 (0.54-0.60)
160–169	443,740	3.1	1.00	1.00
≥ 170	443,740 250,635	5.2	1.75 (1.70–1.79)	1.86 (1.81–1.91)
≥ 170 Missing	250,055 79,166	3.5	1.75 (1.70–1.79)	1.60 (1.61–1.91)
Living with infant's father	79,100	5.5		
Yes	772,673	3.7	1.00	1.00
No	41,755	2.5	0.68 (0.63–0.72)	0.91 (0.85–0.98)
Missing	59,735	3.6	0.08 (0.03-0.72)	0.31 (0.03-0.30)
Country of birth	05,700	0.0		
Nordic	747,284	3.8	1.00	1.00
Non-Nordic	114,376	2.5	0.65 (0.63–0.68)	0.74 (0.71–0.78)
Missing	12,503	2.3	0.03 (0.03-0.08)	0.74(0.71-0.76)
Smoking (cigarettes per day)	12,000	2.4		
0	693,404	3.9	1.00	1.00
1-9	87,086	2.1	0.54 (0.51-0.57)	0.52 (0.49-0.55)
≥ 10	46,355	1.9	0.47 (0.44 - 0.51)	0.32(0.45, 0.33) 0.39(0.36-0.41)
Missing	47,318	3.8	0.47 (0.44 0.51)	0.00 (0.00 0.41)
Gestational diabetes	17,010	0.0		
Yes	7,173	14.1	4.53 (4.23-4.84)	3.35 (3.08-3.63)
No	866,990	3.5	1.00	1.00
Preeclampsia	000,550	0.0	1.00	1.00
Yes	20,610	4.6	1.30 (1.21-1.39)	1.17 (1.08-1.26)
No	853,553	3.6	1.00 (1.21 1.00)	1.00
Gestational age (wk)	000,000	0.0	1.00	1.00
37–41	807,094	95.9	1.00	1.00
≥ 42	67,069	4.2	0.51 (0.48 - 0.54)	0.48 (0.45 - 0.52)
Total	874,163	3.6	0.01 (0.10 0.01)	0.10 (0.10 0.02)

Table 1. Crude and Adjusted Odds Ratios Using 95% Confidence In	ntervals Between Maternal and Pregnancy Character-
istics and Large For Gestational Age Birth*	

* Live singleton births delivered at 37 completed weeks or later.

[†] Large for gestational age birth was defined as a birth weight of more than 2 standard deviations above the mean for that gestational age on the Swedish reference curve.

 * The adjusted model includes all maternal and pregnancy characteristics in this table. It is restricted to births with complete information on age, parity, country of birth, gestational diabetes, preclampsia, gestational age (N = 861,608), and uses mean score regression to account for missing data in the other covariates.

increased odds of giving birth to an LGA infant, respectively (Table 1). The odds of an LGA birth also increased with parity and height. Gestational diabetes was associated with 3-fold increased odds of an LGA birth. Also, as previously documented in term births,¹⁸ preeclampsia was associated with a modest increase in risk.



 Table 2.
 Estimated Odds Ratios* and 95% Confidence Intervals for the Association Between Large for Gestational Age Birth and Calendar Year of Birth After Successively Eliminating Important Confounding Factors From the Fully Adjusted Model

	Adjusted models odds ratio (95% confidence interval)			
Crude odds ratio (95% confidence interval)	Fully adjusted model [†]	Not adjusted for body mass index	Not adjusted for smoking	
1.226 (1.180-1.275)	$1.041 \ (1.000 - 1.084)$	1.219 (1.172 - 1.268)	$1.118 \ (1.074 - 1.164)$	

Values are for years 1992-2001 (linear) 10-year increase.

* Odds ratios reflect increase in risk of large for gestational age births over a 10-year period. All models are restricted to births with complete information on maternal age, parity, country of birth, gestational diabetes, preeclampsia, and length of gestation (N = 861,608) and use mean score regression to account for missing data in the other covariates.

[†]Adjusted for: maternal body mass index, smoking, parity, age, living with infant's father, country of birth, height, preeclampsia, gestational diabetes, and length of gestation.

Without adjusting for maternal and pregnancy characteristics, the relative increase in the odds of LGA birth for a 10-year increase in year of birth (ie, the odds ratio) was 1.23 (Table 2). After adjusting for all maternal and pregnancy characteristics there was no longer evidence of an association; the adjusted odds ratio was 1.04 (95% confidence interval [CI] 1.00-1.08) for a 10-year increase in year of birth. When adjusted for all maternal and pregnancy characteristics other than BMI, the estimated odds ratio was 1.22 (95% CI 1.17-1.27), a relative risk of similar magnitude to the unadjusted estimate. When adjusted for all maternal and pregnancy characteristics other than maternal smoking the odds ratio was 1.12 (95% CI 1.07-1.16).

Our model assumes that the log odds of LGA is a linear function of calendar year, an assumption that can be assessed by plotting the odds ratios estimated for each calendar year (Fig. 2). The top line in Figure 1 indicates a steep increasing odds ratio for LGA birth by successive calendar year and the associated confidence intervals of these odds ratios (with 1992 as the reference category). The bottom line represents the odds ratios of LGA by calendar year while controlling for all variables. The positioning of this line and its confidence intervals around the odds ratio of 1 suggests that the trend tends to disappear, ie, the temporal trend in LGA births is explained by the temporal trend of maternal and pregnancy characteristics included in the analysis.

DISCUSSION

Our data show that mean birth weight, mean birth length, proportion of LGA births, and the proportion of births weighing more than 4,500 g increased in Sweden between 1992 and 2001. These findings confirm and extend results from a hospital-based study in Canada that reported that concurrent trends in maternal characteristics and pregnancy complications explained the increasing proportions of LGA births over time.¹² Our study was population-based, and the results indicate that the most important of these maternal risk factors were BMI and smoking.

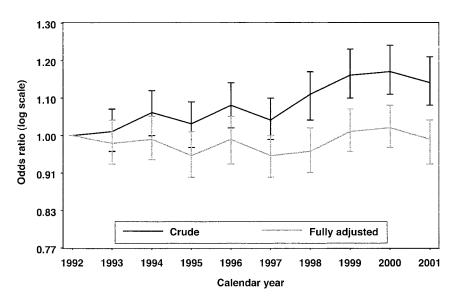


Fig. 2. Trends in odds ratios and 95% confidence intervals (*vertical bars*) for large for gestational age births by year of birth.

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The fact that temporal trends in maternal BMI in large part explain trends in LGA births over time is not surprising. Numerous studies have documented a relation between high maternal BMI and large offspring birth size,¹⁹⁻²¹ and the prevalence of overweight among young women has increased recently.^{22,23} It is thought that obesity reduces insulin sensitivity and increases the availability of glucose available for maternal-fetal transport,²⁴ causing increases in intrauterine growth.²⁵ Another explanation suggests a developmental component. Higher birth weights have been linked to higher BMI in adulthood,^{26,27} and mother's own birth weight predicts offspring birth weight.²⁸ This implies that the temporal trends in increased birth weight may not be entirely due to an increase in mother's BMI, but may also be already determined in part at the time of the mother's birth.

Our study is a population-based study that examines explanatory models for the temporal trends in increase in birth weight. Using the population-based Swedish Birth Registry, we were able to use prospectively collected data to study almost 875,000 singleton term births. We were able to control for simultaneous trends in several maternal characteristics and pregnancy complications. Complete covariate information was available for only 77% of the observations, and the mean score method was used to enable an appropriate analysis of the complete data set.

We did not have information on weight gain during pregnancy or maternal education. Weight gain in pregnancy has been identified as a predictor of high birth weight.²⁹ Other research has found that prepregnancy weight is predictive of high birth weight newborns, but that weight gain during pregnancy is not.²⁴ Nevertheless, despite this potential limitation, Kramer et al¹² found that the inclusion of weight gain during pregnancy model had less of an impact than prepregnancy weight.

Given the worldwide trends of increases in overweight among children and adolescents,^{8,30} LGA births are likely to become an even more serious problem. This study reinforces the importance of women of childbearing age maintaining a normal weight. Our research findings provide additional reason for physicians to encourage their overweight patients to lose weight. A combination of increased physical activity and dietary restriction has shown promise as a method to maintain weight-loss.^{31,32} However, as far as we know, there are presently no successful intervention studies aiming at reducing the prevalence of overweight that can be implemented on a population basis. Our results suggest that addressing the problem of overweight and obesity in women of child bearing age will be an even more important task in the future.

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