Risk of Diabetes Among Young Adults Born Preterm in Sweden

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OBJECTIVE—Previous studies have suggested that preterm birth is associated with diabetes later in life. These studies have shown inconsistent results for late preterm births and have had various limitations, including the inability to evaluate diabetic outpatients or to estimate risk across the full range of gestational ages. Our objective was to determine whether preterm birth is associated with diabetes medication prescription in a national cohort of young adults.

RESEARCH DESIGN AND METHODS—This was a national cohort study of 630,090 infants born in Sweden from 1973 through 1979 (including 27,953 born preterm, gestational age <37 weeks), followed for diabetes medication prescription in 2005–2009 (ages 25.5–37.0 years). Medication data were obtained from all outpatient and inpatient pharmacies throughout Sweden.

RESULTS—Individuals born preterm, including those born late preterm (gestational age 35–36 weeks), had modestly increased odds ratios (ORs) for diabetes medication prescription relative to those born full term, after adjusting for fetal growth and other potential confounders. Insulin and/or oral diabetes medications were prescribed to 1.5% of individuals born preterm compared with 1.2% of those born full term (adjusted OR 1.13 [95% CI 1.02–1.26]). Insulin without oral diabetes medications was prescribed to 1.0% of individuals born preterm compared with 0.8% of those born full term (1.22 [1.08–1.39]).

CONCLUSIONS—Preterm birth, including late preterm birth, is associated with a modestly increased risk of diabetes in young Swedish adults. These findings have important public health implications given the increasing number of preterm births and the large disease burden of diabetes, particularly when diagnosed in young adulthood.

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Low birth weight may result from either preterm birth or fetal growth delay and is associated with diabetes in later life (1,2). Several studies (3–9), but not all (10), that have examined the specific contributions of preterm birth and fetal growth have suggested that preterm birth is an independent risk factor for type 2 diabetes in later life. Others (11,12) have suggested an independent association between early gestational age at birth and type 1 diabetes. These studies have had various limitations, including the use of self-reported diagnoses (4); the use of hospital diagnoses, which excludes the larger number of patients treated in outpatient settings (7); the inability or insufficient power to estimate risk across the full range of gestational ages (3,5,6,8,10–12); or have shown inconsistent results for late preterm births (9). In addition, most of these studies have focused on type 2 diabetes, whereas few studies have examined the specific contribution of preterm birth on the risk of type 1 diabetes.

To address these gaps in the current knowledge, we conducted a national cohort study using nationwide pharmacy data to examine whether preterm birth is associated with increased prescription of insulin and oral diabetes medications in young adulthood (ages 25.5–37.0 years). Diabetes medication data were obtained from 4.5 years of outpatient and inpatient pharmacy records from all health care settings throughout Sweden. Young adults are of particular interest because most diabetes in this age range is type 1 diabetes (13), and a diagnosis of diabetes at this age carries disproportionately high morbidity and mortality (14). We hypothesized that young adults who were born preterm have a higher prevalence of diabetes medication prescription than those who were born full term.

RESEARCH DESIGN AND METHODS

We identified 648,276 individuals in the Swedish Medical Birth Register who were born from 1973 through 1979. Of this total, we excluded 6,553 (1.0%) individuals who were no longer living in Sweden at the time of follow-up (2005–2009), 7,926 (1.2%) who had significant congenital anomalies (i.e., other than undescended testicle, preauricular appendage, congenital nevus, or hip dislocation), and 1,882 (0.3%) who had missing information on birth weight. To remove possible coding errors, we also excluded six (<0.01%) individuals who had a reported gestational age <23 weeks and 1,819 (0.3%) individuals who had a reported birth weight >4 SDs above or below the mean birth weight for gestational age and sex from a Swedish reference growth curve (15). A total of 630,090 individuals (97.2% of the original cohort) remained for inclusion in the study.

Study period

Study participants were followed for diabetes medication prescriptions from 1 July 2005 through 31 December 2009, the first 4.5 years that the national pharmacy register was kept. These individuals were between 25.5 and 37.0 years of age during the follow-up period.

Outcome measurement

Medication prescription data were obtained using a national pharmacy register maintained by the Swedish National Board of Health and Welfare. This register contains a record of each medication prescribed by a health care provider and dispensed to a patient by any outpatient or inpatient pharmacy in Sweden. For inpatients, the register includes all medications

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prescribed to a patient upon discharge from the hospital. All medication data are categorized according to the Anatomical Therapeutic Chemical (ATC) classification system developed by the World Health Organization Collaborating Centre for Drug Statistics Methodology. We obtained all outpatient and inpatient prescriptions for "drugs used in diabetes" (ATC code A10). These data were linked to the national Medical Birth Register using an anonymous identification number. The outcome was defined alternatively as at least one prescription of any diabetes medication (A10) or at least one prescription of insulin (A10A) and no prescriptions of oral diabetes medications (A10B), during the follow-up period.

Exposure measurement

The exposure of interest was gestational age at birth, which was based on maternal report of last menstrual period and categorized as 23–28, 29–34, 35–36, 37–42 (full term), and ≥43 weeks. This information was obtained from prenatal and birth records in a national research database, WomMed, located at the Center for Primary Health Care Research, Lund University, Sweden. Cut points were chosen in order to have adequate numbers in each category for statistical analysis.

Adjustment variables

The WomMed database also contains sociodemographic information for the parents, including age, marital status, and socioeconomic indicators, collected annually starting in 1990. For the current study, sociodemographic characteristics were obtained using the Swedish Population and Housing Census of 1990, the most recent census when the young adults in this study (who were then 11–17 years of age) were still likely to be residing in the same household as their mothers. This information was used to identify maternal characteristics that would reflect the social conditions of these young adults during their upbringing, which may be associated with subsequent risk of diabetes. An anonymous, serial-number version of the personal identification number (similar to the U.S. Social Security number but nearly 100% complete) was used to link the mothers to their children. The following variables were included as potential confounders.

Age. Modeled as a continuous variable by infant's date of birth.

Sex. Female or male.

Maternal age at delivery. This was included because advanced maternal age of <20, 20–24, 25–29, 30–34, or ≥35 years is associated with preterm delivery and with gestational diabetes, which is a risk factor for the development of diabetes in the offspring (16).

Maternal marital status in 1990. Married/cohabiting, never married, divorced, or widowed.

Maternal education in 1990. Compulsory high school or less (≤9 years), practical high school or some theoretical high school (10–11 years), or theoretical high school and/or college (≥12 years).

Family income in 1990. Calculated as the annual family income divided by the number of people in the family or family income per capita, using a weighted system whereby small children were given lower weights than adolescents and adults. The final variable was categorized in quartiles.

Maternal prescription of diabetes medications. Prescription of diabetes medications (ATC code A10) to the mothers of the study participants during the follow-up period, dichotomized as none or one or more prescriptions.

Fetal growth. Birth weight for gestational age and sex was used as a measure of fetal growth, categorized into six groups according to the number of SDs from the mean birth weight for gestational age and sex from a Swedish reference growth curve (<−2 SDs, ≥−2 SDs and <−1 SD, ≥−1 SD and <0 SDs, ≥0 SDs and <1 SD, ≥1 SD and <2 SDs, and ≥2 SDs) (15).

Statistical analysis

Generalized estimating equations were used to estimate odds ratios (ORs) and 95% CIs for the association between gestational age at birth (categorized as 23–28, 29–34, 35–36, 37–42, and ≥43 weeks) and prescription of diabetes medications (as defined above) in young adulthood (ages 25.5–37.0 years), using full-term birth (37–42 weeks) as the reference category. Analyses were conducted unadjusted and then were adjusted in two different models. Adjusted model 1 included the following infant and maternal characteristics as potential confounders: age, sex, maternal age at delivery, maternal marital status, maternal education, family income, and maternal prescription of diabetes medications during the follow-up period. Adjusted model 2 included the same set of variables and fetal growth. Robust SEs were used in all models in order to account for correlation among siblings. We also explored first-order interactions between gestational age at birth and each of the model covariates with respect to diabetes medication prescription in young adulthood, using a likelihood ratio test to evaluate for statistical significance. All analyses were conducted using Stata statistical software, version 11.0 (17).

RESULTS—Of 630,090 individuals who were identified, 27,953 (4.4%) were born prematurely (gestational age <37 weeks), including 419 (0.1%) born at 23–28 weeks, 8,509 (1.4%) born at 29–34 weeks, and 19,025 (3.0%) born at 35–36 weeks. Compared with individuals who were born full term, those who were born prematurely were more likely to be male, and their mothers were more likely to be aged <20 or ≥35 years at the time of delivery, to be divorced or never married, to have the lowest educational attainment and lowest family incomes, and/or to be prescribed diabetes medications during the follow-up period (data not shown).

A higher prevalence of any diabetes medication or of only insulin prescription was observed among individuals born preterm (gestational age <37 weeks), including among those born late preterm (35–36 weeks), compared with those born full term (Table 1). A total of 7,751 (1.2%) young adults from the entire cohort were prescribed at least one diabetes medication, including 1.5% of those born at 35–36 weeks, 1.4% of those born at 29–34 weeks, and 1.9% of those born at 23–28 weeks' gestation. A total of 4,997 (0.8%) individuals were prescribed insulin without being prescribed oral diabetes medications during the study period, including 1.0% of those born at either 35–36 weeks or 29–34 weeks, and 1.2% of those born at 23–28 weeks' gestation.

Young adults who were born preterm, including those born late preterm (35–36 weeks' gestation), had modestly increased relative odds of diabetes medication prescription (Table 2). Adjustment for potential confounders, with or without fetal growth, had only modest effects on the ORs. In the fully adjusted model, comparing young adults born preterm (<37 weeks' gestation) to those born full term, the OR for any diabetes medication prescription was 1.13 (95% CI 1.02–1.26) and for insulin without oral diabetes medication prescription 1.22 (1.08–1.39). Higher ORs were observed

Table 1—*Diabetes medication prescription in young adulthood (ages 25.5–37.0 years) by gestational age at birth (1973–1979)*

Medications (ATC code)	Gestational age						
	<37 weeks	23–28 weeks	29–34 weeks	35–36 weeks	37–42 weeks	≥43 weeks	All
n	27,953	419	8,509	19,025	583,571	18,566	630,090
Any diabetes medications (A10)	407 (1.5)	8 (1.9)	117 (1.4)	282 (1.5)	7,103 (1.2)	241 (1.3)	7,751 (1.2)
Any insulin (A10A) without oral diabetes medications (A10B)	278 (1.0)	5 (1.2)	86 (1.0)	187 (1.0)	4,587 (0.8)	132 (0.7)	4,997 (0.8)

Data are *n* (%).

for young adults born extremely preterm (23–28 weeks' gestation), but the small number of these individuals and the low background prevalence of diabetes in young adulthood resulted in wider CIs for these estimates. Modestly increased ORs were observed for young adults born at 29–34 weeks and 35–36 weeks' gestation, and there was little difference in risk estimates across this gestational age range.

A weak association also was found between poor fetal growth and diabetes medication prescription in young adulthood. After adjusting for gestational age at birth and the other potential confounders included in adjusted model 1, ORs were 1.41 (95% CI 1.26–1.59) and 1.13 (1.06–1.21) for the two smallest fetal growth categories (<−2 SDs and ≥−2 SDs and <−1 SD, respectively), relative to individuals with fetal growth ≥0 SDs and <1 SD from the reference using a standard Swedish growth curve (15). No first-order interactions were statistically significant at the $P < 0.01$ level, including no interaction between gestational age at birth and fetal growth ($P = 0.33$).

CONCLUSIONS—These findings based on nationwide outpatient and inpatient medication data show that individuals who are born prematurely, including the large numbers who are born late preterm, have an increased risk of diabetes in young adulthood. This association was independent of fetal growth. Most diabetes in this cohort was likely type 1 diabetes, as identified by the prescription of insulin without any oral diabetes medications. The highest relative odds were observed for young adults born extremely preterm (23–28 weeks' gestation), although the precision of these estimates was limited as a result of the relatively small number of these individuals who have now reached young adulthood. Larger effect sizes and disease burden may be expected in older populations as increasing numbers of individuals who were born preterm continue to age.

The modestly increased risk of diabetes in young adulthood that was observed in this study may have a disproportionately large public health impact as a result of the high morbidity and mortality that tend to follow diabetes when diagnosed at this age. It is estimated that a diagnosis of diabetes at the age of 40 years, for example, is associated with a loss of 11.6 and 14.3 life-years for men and women, respectively (14). In addition, most diabetes in young adulthood is type 1 diabetes, which incurs a disproportionately high economic burden in terms of medical costs and lost income (18).

The observed association between late preterm birth (35–36 weeks' gestation) and diabetes medications in young adulthood also has important implications. The total prevalence of preterm birth is 12–13% in the U.S., (19) similar to that in Africa (20) or Brazil (21), compared with 4–9% in Europe (19). Late preterm births constitute approximately two-thirds of this total in the current study and in other populations (19). Given the large and increasing number of late preterm births, even a modestly increased risk of diabetes among these individuals may have a large public health impact.

These results are compatible with most previous smaller studies of preterm birth and either type 1 or type 2 diabetes. A study of 72 children aged 4–10 years reported that those born preterm, regardless of whether appropriate or small for gestational age, had decreased insulin sensitivity compared with children born full term and appropriate for gestational age (3). Another study of 332 adults aged 18–27 years reported that individuals born preterm, regardless of whether small or appropriate for gestational age, had increased insulin resistance and glucose

Table 2—*ORs for association between gestational age at birth (1973–1979) and diabetes medication prescription in young adulthood (ages 25.5–37.0 years)*

Medications (ATC code) (outcome variable)	Unadjusted OR (95% CI)	Adjusted model 1* OR (95% CI)	Adjusted model 2† OR (95% CI)
Any diabetes medications (A10)			
Gestational age (predictor variable) (weeks)			
<37	1.20 (1.08–1.33)	1.16 (1.04–1.28)	1.13 (1.02–1.26)
23–28	1.56 (0.77–3.18)	1.54 (0.76–3.15)	1.53 (0.75–3.11)
29–34	1.13 (0.93–1.36)	1.09 (0.90–1.32)	1.05 (0.87–1.28)
35–36	1.22 (1.08–1.38)	1.18 (1.04–1.33)	1.16 (1.03–1.31)
37–42	1.00	1.00	1.00
≥43	1.07 (0.94–1.21)	1.03 (0.90–1.17)	0.98 (0.86–1.11)
Any insulin (A10A) without oral diabetes medications (A10B)			
Gestational age (predictor variable) (weeks)			
<37	1.26 (1.12–1.43)	1.24 (1.09–1.40)	1.22 (1.08–1.39)
23–28	1.53 (0.64–3.70)	1.52 (0.63–3.67)	1.51 (0.63–3.65)
29–34	1.28 (1.03–1.61)	1.26 (1.00–1.57)	1.25 (1.00–1.56)
35–36	1.25 (1.08–1.45)	1.22 (1.05–1.42)	1.21 (1.04–1.40)
37–42	1.00	1.00	1.00
≥43	0.90 (0.76–1.08)	0.90 (0.75–1.07)	0.90 (0.76–1.08)

*Adjusted for age, sex, maternal age at delivery, maternal marital status, maternal education, family income, and maternal prescription of diabetes medications during the follow-up period (1 July 2005 through 31 December 2009). †Adjusted for the same variables included in adjusted model 1 and fetal growth.

intolerance compared with those born full term and appropriate for gestational age (5). A study of 87 young adults, average age 22 years, confirmed these findings (6), although a study of 305 young adults aged 18–24 years did not (10). There are fewer data on the specific contribution of gestational age at birth on risk of type 1 diabetes, but two relatively large studies of individuals aged <15 years reported an association between gestational age <37 weeks (11) or <39 weeks (12) and type 1 diabetes, after adjusting for birth weight.

The few studies to date of middle-aged or older adults have consistently reported an association between preterm birth and type 2 diabetes. A Danish study of 4,744 individuals aged 30–60 years reported that preterm birth, independent of fetal growth, was associated with type 2 diabetes diagnosed by an oral glucose tolerance test (8). A Swedish study of 6,425 individuals born from 1925 to 1949 reported that preterm birth was associated with a diagnosis of diabetes as identified from hospital discharge records from 1987 to 2006 (ages 38–81 years) (7). Unlike our study, diabetes was ascertained solely from hospital discharge data, which did not include the larger number of diabetic patients treated in outpatient settings. A U.K. study of 5,792 adults aged 46–50 years reported that preterm birth was associated with self-report of a physician's diagnosis of diabetes after age 20 years (4). A Finnish study of 12,731 adults born between 1934 and 1944 reported that preterm birth at gestational age <35 weeks was associated with special reimbursement for diabetes medication after 40 years of age (9). However, in contrast to the current study, late preterm birth (35 to <37 weeks' gestation) in that study was associated with a nonsignificantly lower risk of diabetes medication reimbursement.

Previous evidence for an association between low birth weight and insulin resistance led to the fetal origins hypothesis that fetal undernutrition in middle and late gestation triggers hormonal and metabolic changes that lead to lasting insulin resistance and diabetes (22). Experimental (23) and clinical (24) data have shown that prenatal and/or postnatal dietary restriction predisposes individuals to persistent abnormalities in glucose regulation. Additional research on the effects of perinatal nutrition and growth patterns on glucose metabolism and autoimmune responses is needed to clarify the etiologic pathways.

One limitation of the current study is the use of diabetes medication prescriptions as a surrogate measure for diabetes. This approach fails to identify individuals who have diabetes but remain undiagnosed and those who are not medically treated. If this occurs nondifferentially with respect to preterm birth status, it biases the results toward the null hypothesis, in which case the reported ORs in the current study would underestimate the true effect sizes. We are unable to exclude the possibility of diagnostic or prescription bias among individuals in this cohort who were born preterm. However, the prevalence of diabetes medication prescription in this study was similar to previously published prevalences of diabetes in the same age range in Sweden using World Health Organization diagnostic criteria (25), suggesting that the amount of bias, if any, is small.

Gestational diabetes, maternal weight, and/or postnatal growth patterns may be important potential modifiers of the effect of preterm birth on diabetes in later life, and this information was unavailable for this cohort. Another limitation is the estimation of gestational age by maternal report of last menstrual period rather than by ultrasound, which was not yet widely used at the time these study participants were born (1973–1979). To reduce misclassification, we excluded individuals whose birth weight deviated >4 SDs from the mean reference birth weight for gestational age and sex. Any remaining misclassification is expected to be nondifferential with respect to preterm birth status and therefore to bias the results toward the null hypothesis.

The most important strength of this study is its ability to examine the association between preterm birth and diabetes in a large national cohort using nationwide outpatient as well as inpatient medication data. These data are remarkably complete because they are obtained from all outpatient and inpatient pharmacies from all health care settings throughout Sweden, thus avoiding bias that may result either from self-reporting or from the sole use of hospital-based data. This also was a very large study, which was essential for improving statistical power, which would otherwise be limited because of the low background prevalence of diabetes in a young-adult population. Most diabetes identified in this cohort was type 1 diabetes, which has been relatively understudied.

In summary, this national cohort study shows that preterm birth, including late preterm birth, is associated with an increased risk of diabetes in young Swedish adults. These findings have important public health implications because of the high morbidity and mortality associated with diabetes when diagnosed in young adulthood. Larger effect sizes and a larger burden of disease may be expected as increasing numbers of individuals born preterm continue to age. Additional research on the effects of perinatal nutrition and growth patterns on glucose metabolism and autoimmune responses is needed to elucidate the etiologic mechanisms. Improved recognition of diabetes and other cardiovascular risk factors among individuals born preterm is an urgent priority and may lead to earlier interventions to prevent disease.

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C.C. conceived the study, analyzed and interpreted data, drafted the article, and approved the final version. M.A.W., K.S., and J.S. made substantial contributions to the study design, data interpretation, manuscript revisions, and approval of the final version.

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