Risk of Asthma in Young Adults Who Were Born Preterm: A Swedish National Cohort Study

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KEY WORDS

adult, asthma, premature birth

ABBREVIATIONS

ATC—Anatomical Therapeutic Chemical

OR—odds ratio

CI—confidence interval

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WHAT'S KNOWN ON THIS SUBJECT: Preterm birth is associated with chronic lung disease in infancy and asthma-like symptoms in later childhood. The longer-term risk of asthma in children born preterm, however, is unclear and increasingly relevant as larger numbers of these individuals are entering adulthood.

WHAT THIS STUDY ADDS: This is the first study with sufficient statistical power to evaluate asthma risk in young adults born extremely preterm. Extreme, but not later, prematurity is identified as a new, potentially important risk factor for asthma, at least into young adulthood.

abstract

OBJECTIVE: Preterm birth is associated with asthma-like symptoms in childhood and possibly in adolescence, but the longer-term risk of asthma is unknown and increasingly relevant as larger numbers of these individuals enter adulthood. Our objective was to evaluate whether those who were born preterm are more likely to be prescribed asthma medications in young adulthood than those who were born term.

PATIENTS AND METHODS: We conducted a national cohort study of all singleton infants born in Sweden from 1973 through 1979 ($n = 622\,616$), followed to ages 25.5 to 35.0 years to determine whether asthma medications were prescribed in 2005–2007. Asthma medication data were obtained from all outpatient and inpatient pharmacies throughout Sweden. To improve the positive predictive value for asthma, the outcome was defined as prescription of (1) both a β -2 agonist inhalant and a glucocorticoid inhalant or (2) a combination inhalant containing a β -2 agonist and other drugs for obstructive airway diseases.

RESULTS: Young adults who were born extremely preterm (23–27 weeks' gestation) were 2.4 times more likely (adjusted 95% CI: 1.41–4.06) to be prescribed asthma medications than those who were born term. No association was found between later preterm birth (28–32 or 33–36 weeks' gestation) and asthma medications in young adulthood.

CONCLUSIONS: This is the first study with sufficient statistical power to evaluate the risk of asthma beyond adolescence in individuals who were born extremely preterm. The results suggest that extreme preterm birth (23–27 weeks' gestation), but not later preterm birth, is associated with an increased risk of asthma at least into young adulthood. *Pediatrics* 2011;127:e913–e920

Preterm birth is associated with chronic lung disease in infancy and the development of asthma-like symptoms in later childhood.¹ The longer-term risk of asthma after preterm birth, however, is unclear and increasingly relevant as larger numbers of these individuals now are entering adulthood. It is previously assumed that a “trend toward clinical improvement is usually seen over time . . . symptoms progressively subside, respiratory exacerbations become uncommon, and most persons lead apparently normal lives” (p 1948).¹ Until now, data with which to evaluate this assumption are very limited, and the few previous studies^{2–5} of this topic in young adults have yielded mixed results.

We conducted a national cohort study to evaluate whether young adults who were born preterm are more likely to be prescribed asthma medications than those who were born term. Young adults are an especially appropriate age group for the use of asthma medications as a surrogate measure for asthma, because they have a lower incidence of nonasthma conditions for which these medications are prescribed, such as respiratory infections associated with wheezing (which are more common in children) or chronic obstructive pulmonary disease (which is more common in older adults). We obtained asthma medication data from nationwide outpatient and inpatient pharmacy records from all health care settings throughout Sweden during 2.5 years of follow-up. To our knowledge, this is the largest study to date of the association between preterm birth and the subsequent risk of asthma and the first study with sufficient statistical power to estimate this risk in young adults who were born extremely preterm.

PATIENTS AND METHODS

Study Population

A total of 637 604 women and men were identified in the Swedish Medical Birth Register who were born as sin-

gletons from 1973 through 1979. Of this total, we excluded 3741 (0.6%) subjects who were no longer living in Sweden at the time of follow-up (2005–2007), 7721 (1.2%) subjects who had significant congenital anomalies (ie, other than undescended testicle, preauricular appendage, congenital nevus, or hip dislocation), and 1828 (0.3%) subjects who had missing information on birth weight. To remove possible coding errors, we also excluded 6 (<0.01%) subjects who had a reported gestational age of less than 23 weeks and 1692 (0.3%) subjects who had a reported birth weight more than 4 SDs above or below the mean birth weight for gestational age and gender from a Swedish reference growth curve.⁶ A total of 622 616 subjects (97.6% of the original cohort) remained for inclusion in the study. This study was approved by the ethics committee of Lund University, Malmö, Sweden.

Study Period

All study participants were followed for prescription of asthma medications from July 1, 2005, through December 31, 2007, the first 2.5 years that the Swedish National Pharmacy Register was kept. These individuals were between 25.5 and 35.0 years of age during the period of follow-up.

Outcome Measurement

Asthma medication prescription data were obtained using a national pharmacy register maintained by the National Board of Health and Welfare.⁷ This register contains a record of each medication that is prescribed by a health care provider and dispensed to a patient by any outpatient or inpatient pharmacy in Sweden; for brevity, “prescriptions” will hereafter refer to prescriptions that were both written and dispensed. For inpatients, the register includes all medications prescribed and dispensed to a patient upon discharge from the hospital. All medica-

tion data are categorized according to the Anatomic Therapeutic Chemical (ATC) Classification System developed by the World Health Organization Collaborating Centre for Drug Statistics Methodology.⁸ We obtained information on medications prescribed for obstructive airway diseases (ATC code R03), which were subclassified as selective β -2 adrenoreceptor agonist inhalants (R03AC), combination inhalants containing a β -2 agonist and other drugs for obstructive airway diseases (R03AK03 through R03AK07), and glucocorticoid inhalants (R03BA). These data were linked to the Medical Birth Register using an anonymous identification number.

The primary outcome of interest was defined by the following criteria: (1) at least 1 prescription of a β -2 agonist inhalant (R03AC) and at least 1 prescription of a glucocorticoid inhalant (R03BA) or (2) at least 1 prescription of a combination inhalant containing a β -2 agonist and other drugs for obstructive airway diseases (R03AK03 through R03AK07) during the follow-up period. Single agents, such as a β -2 agonist, also are prescribed for nonasthma conditions such as respiratory infections associated with wheezing and, therefore, were not evaluated separately. Evaluation of combinations of these medication classes has been shown to improve their positive predictive value for asthma.^{9,10} Note that the combination inhalants containing a β -2 agonist and other drugs for obstructive airway diseases (R03AK03 through R03AK07) are not further specified in the ATC coding system. Most of these, especially in a young adult population, would be expected to contain a glucocorticoid as the other drug. As a secondary outcome, we evaluated the number of prescriptions of any drug for obstructive airway diseases (R03) as count data.

We also evaluated oral contraceptives as a control medication. Oral contraceptive prescription in young adulthood is not a priori expected to be associated with preterm birth status. If an association were found between preterm birth and asthma medications in young adulthood, and not between preterm birth and oral contraceptives, the association with asthma medications is less likely to be attributable to diagnostic bias among subjects who were born preterm. Oral contraceptives (ATC code G03A) were dichotomized as at least 1 prescription or no prescriptions during the same follow-up period, as noted above.

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 to 27 weeks, 28 to 32 weeks, 33 to 36 weeks, 37 to 42 weeks (full-term), and 43 weeks or more. This information was obtained from register data in a national research database, WomMed, located at the Center for Primary Health Care Research (Lund University, Lund, Sweden). This database contains annual data from prenatal and birth records, hospital admissions, and death records for each mother and child in Sweden. Prenatal and birth records are available for nearly 99% of all births in Sweden.

Adjustment Variables

The WomMed database also contains individual-level sociodemographic information for the parents, including age, marital status, and socioeconomic indicators, collected annually starting in 1990. For the current study, sociodemographic characteristics were identified 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 asthma. The following variables were 100% complete for this cohort and were adjusted for as potential confounders of the association between preterm birth and asthma medication prescription in young adulthood:

1. Date of birth: Modeled as a continuous variable. We included this to adjust for age and changes in perinatal care that may have occurred during the period that these study participants were born (1973–1979).
2. Gender: Female or male.
3. Fetal growth: Birth weight for gestational age and gender was used as a measure of fetal growth, categorized into 6 groups according to the number of SDs from the mean birth weight for gestational age and gender from a Swedish reference growth curve (< -2 SDs, ≥ -2 SDs and < -1 SD, ≥ -1 SD and < 0 SD, ≥ 0 SD and < 1 SD, ≥ 1 SD and < 2 SDs, and ≥ 2 SDs).⁶
4. Maternal marital status in 1990: Married/cohabiting, never married, divorced, or widowed.
5. 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).
6. 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 are given lower weights than adolescents and

adults. The final variable was categorized in quartiles.

7. Maternal prescription of asthma medications: Prescription of asthma medications (β -2 agonist inhalants, glucocorticoid inhalants, or combination inhalants containing a β -2 agonist and other drugs for obstructive airway diseases) to the mothers of the study participants during the follow-up period (July 1, 2005, through December 31, 2007). Each of these medication classes was dichotomized as at least 1 prescription or no prescriptions and was entered into the model separately.

Statistical Analysis

Generalized estimating equations were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the association between gestational age at birth (23–27 weeks, 28–32 weeks, 33–36 weeks, 37–42 weeks, and ≥ 43 weeks) and prescription of asthma medications (as defined above) in young adulthood (ages 25.5–35.0 years), using term birth (37–42 weeks' gestation) as the reference category. Analyses were conducted unadjusted and then were adjusted for infant and maternal characteristics (as defined above) that are potential confounders. In a secondary analysis, negative binomial regression (a standard method for analyzing count data that are overdispersed) was used to estimate incidence rate ratios and 95% CIs for the association between gestational age at birth (as defined above) and the number of prescriptions of any drug for obstructive airway diseases (ATC code R03) as count data. Robust SEs were used in all models to account for correlation among siblings. We also explored for first-order interaction effects between gestational age at birth and each of the model covariates with respect to asthma medication

TABLE 1 Infant and Maternal Characteristics by Gestational Age At Birth (1973–1979)

	Gestational Age, %, wk				
	23–27, n = 165	28–32, n = 2657	33–36, n = 21 918	37–42, n = 579 359	≥43, n = 18 517
Gender					
Male	54.6	56.9	56.0	51.3	50.1
Female	45.4	43.1	44.0	48.7	49.9
Maternal marital status in 1990					
Married/cohabiting	73.5	69.9	71.1	76.3	72.9
Never married	14.2	13.1	12.4	9.5	11.4
Divorced	12.3	16.2	15.1	13.0	14.6
Widowed	0.0	0.7	1.4	1.2	1.0
Family income in 1990					
Lowest quartile	30.9	28.8	26.6	23.0	24.0
Second quartile	21.2	24.8	25.6	25.8	25.3
Third quartile	25.5	25.2	24.9	25.7	25.9
Highest quartile	22.4	21.2	22.9	25.5	24.8
Maternal education in 1990					
Compulsory high school or less (≤9 years)	30.3	31.5	31.6	26.9	29.5
Practical high school or some theoretical high school (10–11 years)	46.9	47.6	46.7	47.2	47.4
Theoretical high school and/or college (≥12 years)	22.8	20.8	21.7	25.8	23.0
Maternal prescription of asthma medications ^a from July 1, 2005, through December 31, 2007	10.3	9.1	9.0	7.6	8.4

^a Defined as (1) both a β -2 agonist inhalant (R03AC) and a glucocorticoid inhalant (R03BA) or (2) a combination inhalant containing a β -2 agonist and other drugs for obstructive airway diseases (R03AK03 through R03AK07).

prescription in young adulthood, using a likelihood ratio test to evaluate for statistical significance. All analyses were conducted using Stata statistical software, version 11.0.¹¹

RESULTS

Subject Characteristics

Of 622 616 subjects who were identified, 24 740 (4.0%) were born prematurely (<37 weeks' gestation), including 165 (0.03%) subjects born at 23 to 27 weeks, 2657 (0.4%) born at 28 to 32 weeks, and

21 918 (3.5%) born at 33 to 36 weeks (Table 1). Compared with individuals who were born term or postterm, those who were born prematurely were more likely to be male and their mothers were more likely to be unmarried, to be less educated, have lower income, and/or be prescribed asthma medications during the follow-up period.

Main Analyses

Young adults born extremely preterm (23–27 weeks's gestation) had the

highest proportion who were prescribed asthma medications, regardless of how these medications were defined (Table 2). The proportion of subjects who were prescribed asthma medications was relatively constant across the range of other gestational ages (28–43 or more weeks' gestation). A total of 46 589 (7.5%) subjects were prescribed any medication for obstructive airway diseases (ATC code R03). A total of 25 117 (4.0%) subjects were prescribed both a β -2-agonist and a glucocorticoid inhalant or a combination inhalant containing a β -2 agonist and other drugs for obstructive lung diseases, including 9.1% of those who were born extremely preterm (23–27 weeks' gestation) compared with 3.8% to 4.0% in the other gestational-age groups. There was no clear relationship between prescription of the control medication (oral contraceptives) and gestational age at birth.

We found a significant association between extreme preterm birth and asthma medication prescription in young adulthood (Table 3). With or without adjustment for other variables (see Table 3 footnote), young adults who were born at gestational ages 23 to 27 weeks were 2.4 times more likely (adjusted 95% CI: 1.41–4.06) to be prescribed both a β -2 agonist and a glucocorticoid inhalant or a combination inhalant containing a β -2 agonist and other drugs for obstructive lung dis-

TABLE 2 Asthma Medication Prescription in Young Adulthood (Ages 25.5–35.0 Years) by Gestational Age At Birth (1973–1979)

Medications (ATC Code)	Gestational Age, n (%), wk					
	23–27, n = 165	28–32, n = 2657	33–36, n = 21 918	37–42, n = 579 359	≥43, n = 18 517	All, n = 622 616
(1) Both a β -2 agonist inhalant and a glucocorticoid inhalant, or (2) a combination inhalant containing a β -2 agonist and other drugs for obstructive airway diseases ([R03AC and R03BA] or R03AK03-07)	15 (9.1)	102 (3.8)	860 (3.9)	23 423 (4.0)	717 (3.9)	25 117 (4.0)
Both a β -2 agonist inhalant and a glucocorticoid inhalant (R03AC and R03BA)	10 (6.1)	69 (2.6)	575 (2.6)	15 705 (2.7)	465 (2.5)	16 824 (2.7)
Combination inhalant containing a β -2 agonist and other drugs for obstructive airway disease (R03AK03-07)	6 (3.6)	39 (1.5)	359 (1.6)	9714 (1.7)	311 (1.7)	10 429 (1.7)
Oral contraceptives (G03A) (control medication)	35 (21.2)	553 (20.8)	4869 (22.2)	144 305 (24.9)	4540 (24.5)	154 302 (24.8)

TABLE 3 ORs for Association Between Gestational Age At Birth (1973–1979) and Asthma Medication Prescription in Young Adulthood (Ages 25.5–35.0 Years)

Medications (ATC Code), Outcome Variable	Gestational Age, Predictor Variable, wk	Unadjusted OR (95% CI)	Adjusted OR (95% CI) ^a
(1) Both a β -2 agonist inhalant and a glucocorticoid inhalant or (2) a combination inhalant containing a β -2 agonist and other drugs for obstructive airway diseases ([R03AC and R03BA] or R03AK03-07)	23–27	2.38 (1.40–4.04)	2.39 (1.41–4.06)
	28–32	0.95 (0.78–1.16)	0.95 (0.77–1.15)
	33–36	0.97 (0.90–1.04)	0.97 (0.90–1.04)
	37–42	1.00	1.00
	≥43	0.96 (0.89–1.03)	0.95 (0.88–1.03)
Both a β -2 agonist inhalant and a glucocorticoid inhalant (R03AC and R03BA)	23–27	2.32 (1.23–4.40)	2.33 (1.23–4.40)
	28–32	0.96 (0.75–1.22)	0.95 (0.75–1.21)
	33–36	0.97 (0.89–1.05)	0.97 (0.89–1.05)
	37–42	1.00	1.00
	≥43	0.92 (0.84–1.01)	0.92 (0.84–1.01)
Combination inhalant containing a β -2 agonist and other drugs for obstructive airway diseases (R03AK03-07)	23–27	2.22 (0.98–5.00)	2.23 (0.99–5.02)
	28–32	0.87 (0.64–1.20)	0.87 (0.63–1.20)
	33–36	0.98 (0.88–1.09)	0.98 (0.88–1.09)
	37–42	1.00	1.00
	≥43	1.00 (0.89–1.12)	0.99 (0.88–1.11)
Oral contraceptives (G03A), control medication	23–27	0.81 (0.56–1.18)	0.82 (0.52–1.30)
	28–32	0.79 (0.72–0.87)	0.90 (0.80–1.01)
	33–36	0.86 (0.83–0.89)	0.98 (0.94–1.02)
	37–42	1.00	1.00
	≥43	0.98 (0.95–1.01)	0.96 (0.92–1.00)

^a Adjusted for date of birth, gender, fetal growth, maternal marital status, maternal education, family income, and maternal prescription of asthma medications during the follow-up period (July 1, 2005, through December 31, 2007).

eases, compared with young adults born term. No association was found between later preterm birth (gestational ages 28–32 weeks or 33–36 weeks) or postterm birth (≥43 weeks) and asthma medications in young adulthood. Adjusting for any combination of variables included in Table 1 had virtually no effect on any of the OR estimates. No association was found between gestational age at birth and the control medication (oral contraceptives). Although a relatively small number of those born extremely preterm were women, the adjusted 95% CI for oral contraceptive prescription in this group (0.52–1.30) was still well below that for the main asthma medication outcome.

Secondary Analyses

Analysis of the total number of any medication prescriptions for obstructive airway disease (ATC code R03) as count data produced very similar results compared with the main analyses. Young adults who were born extremely preterm had more than twice

the prescription rate relative to those who were born term (adjusted OR: 2.32 [95% CI: 1.28–4.18]), and no association was found between later preterm birth and this outcome (data not shown).

We evaluated other possible cut points for gestational-age groups. No consistent association was found between preterm birth and asthma medications across any part of the gestational age range of 28 to 36 weeks, whereas a consistent increased risk of asthma medication prescription was found across the gestational-age range of 23 to 27 weeks, compared with individuals who were born term.

Table 4 presents ORs and 95% CIs for the association between each categorical covariate and the main outcome (prescription of both a β -2 agonist and a glucocorticoid inhalant or a combination inhalant containing a β -2 agonist and other drugs for obstructive lung diseases). None of the covariates

was a significant predictor of this outcome after adjusting for the other variables in the model.

We explored for first-order interactions between gestational age at birth and each of the covariates with respect to asthma medication prescription in young adulthood. No interactions were statistically significant at the $P < .01$ level.

DISCUSSION

We found that extreme preterm birth was associated with more than a twofold-increased risk of asthma medication prescription in young adulthood compared with term birth. Later preterm or postterm birth was not associated with asthma medication prescription. These findings from a large national cohort identify extreme prematurity, but not later prematurity, as a new potentially important risk factor for asthma, at least into young adulthood. Recognition of this risk factor by clinicians and patients may lead to better detection and treatment of asthma in susceptible individuals throughout their life course.

The few previous studies of association between preterm birth and asthma in young adults are much smaller and did not evaluate extreme preterm birth. A cross-sectional survey study of 690 randomly sampled Norwegian adults aged 20 to 24 years (including only 24 subjects who were born preterm)⁴ and a retrospective study of 567 British adults aged 18 to 25 years, who were registered in general medical practices (including only 31 who were born preterm),² reported a nonsignificant association between preterm birth and self-reported asthma symptoms or an asthma diagnosis on medical chart review, respectively. A population-based survey study of 5192 Finnish adults aged 31 years (including 247 subjects who were born preterm) did not confirm an associa-

TABLE 4 Adjusted ORs^a for Association Between Model Covariates and Asthma Medication Prescription^b in Young Adulthood (Ages 25.5–35.0 Years)

	OR (95% CI)	P
Gender		
Female	1.00	
Male	1.00 (0.97–1.02)	.95
Fetal growth		
<–2 SDs	1.08 (1.00–1.16)	.07
≥–2 SDs and <–1 SD	1.02 (0.98–1.06)	.39
≥–1 SD and <0 SD	1.03 (1.00–1.06)	.06
≥0 SD and <1 SD	1.00	
≥1 SD and <2 SDs	1.03 (0.99–1.07)	.19
≥2 SDs	0.98 (0.92–1.05)	.57
Maternal marital status in 1990		
Married/cohabiting	1.00	
Never married	0.99 (0.95–1.04)	.80
Divorced	0.97 (0.93–1.01)	.13
Widowed	1.07 (0.96–1.20)	.22
Maternal education in 1990, y		
Compulsory high school or less (≤9)	1.00	
Practical high school or some theoretical high school (10–11)	0.98 (0.95–1.01)	.28
Theoretical high school and/or college (≥12)	0.99 (0.95–1.03)	.56
Family income in 1990		
Lowest quartile	1.00	
Second quartile	1.01 (0.98–1.05)	.48
Third quartile	0.99 (0.96–1.03)	.74
Highest quartile	0.98 (0.94–1.02)	.34
Maternal prescription of asthma medications ^b during follow-up period		
0	1.00	
≥1	0.99 (0.94–1.04)	.61

^a This model included gestational age at birth, date of birth, gender, fetal growth, maternal marital status, maternal education, family income, and maternal prescription of asthma medications during the follow-up period (July 1, 2005, through December 31, 2007).

^b Defined here as (1) both a β -2 agonist inhalant and a glucocorticoid inhalant or (2) a combination inhalant containing a β -2 agonist and other drugs for obstructive airway diseases ([R03AC and R03BA] or R03AK03-07).

tion between preterm birth and a self-report of physician-diagnosed asthma.³ A retrospective cohort study of 149 398 Swedish male conscripts aged 17 to 20 years (including 7876 subjects who were born preterm) also did not confirm an association between preterm birth and physician-diagnosed asthma on the basis of a medical interview at a compulsory military examination.⁵ Each of these studies was either unable to evaluate or did not report results for individuals who were born extremely preterm.

Studies of children and adolescents (up to 18 years old) are more numerous and most,^{12–26} but not all,^{27–33} have suggested an association between preterm birth and asthma. A meta-analysis of 19 studies, most of which focused on children and adolescents, found an overall OR of 1.07 for risk of

asthma comparing individuals born at gestational ages less than 37 weeks to those born at 37 weeks or more.³⁴ More detailed results for extreme preterm birth, however, were not available.

Proposed mechanisms by which preterm birth may affect subsequent risk of asthma involve genetic, perinatal, and environmental factors. Premature delivery results in loss of the normal structural complexity of the lung and greater susceptibility to subsequent injury from infection or environmental factors such as smoking.¹ Genetic susceptibility factors also play a role in reduced immunologic regulation needed for normal lung development and function.¹ It is possible that preterm birth and asthma have common genetic determinants.³⁴ There is some evidence

that maternal asthma may be associated with preterm delivery^{25,35} and that maternal asthma is associated with increased risk of asthma in their children.^{36,37}

The current study has several limitations and strengths. One potential limitation is the use of asthma medication prescriptions as a surrogate measure for asthma. There are several features of this study, however, that enhance the validity of this as a proxy. First, as noted, asthma medications are expected to have their highest validity as a surrogate measure for asthma in a young adult population. β -2 Agonist and/or glucocorticoid inhalants are used to treat nonasthma conditions, such as respiratory infections associated with wheezing or chronic obstructive pulmonary disease, but young adults have a lower incidence of these conditions than children or older adults, respectively.¹⁰ Second, the positive predictive value of asthma medications (the proportion of individuals identified who actually have asthma) is improved by using criteria that include multiple classes of asthma medications or multiple prescriptions.^{9,10} Third, the sensitivity of asthma medications as a proxy for asthma (the proportion of asthmatics correctly identified) is enhanced by the availability of data from 2.5 years of follow-up, sufficiently long to detect a very high percentage of the individuals who have asthma.¹⁰

Other limitations include, first, the possibility of diagnostic bias. It is possible that individuals who were born extremely preterm were more likely to be treated for asthma because of greater contact with the health care system for comorbidities. We explored this possibility by analyzing oral contraceptives as a control medication. In contrast to the results for asthma medications, no association was observed between preterm birth and

oral contraceptives, suggesting that it is unlikely that the observed associations between extreme prematurity and asthma medications are attributable to diagnostic bias. Second, estimation of gestational age was on the basis of maternal report of the last menstrual period rather than by ultrasound, which was not yet widely used at the time these study participants were born (1973–1979). Finally, the use of pharmacy data in this study did not allow for the inclusion of nonmedicated cases of asthma, which are perhaps mediated by nonatopic mechanisms and warrant additional study.

This study also has several unique strengths. To our knowledge, it is the largest study to date of the association between preterm birth and the subsequent risk of asthma and the first study with sufficient statistical power to evaluate this risk in young adults born extremely preterm (gestational age 23–27 weeks). Young adults are a relatively understudied age group, as well as the most appropriate

age group for the use of asthma medications as a surrogate measure for asthma. Asthma medication data were obtained from all outpatient and inpatient pharmacies in all health care settings throughout Sweden, thus avoiding the possibility of self-reporting bias. Combinations of asthma medications from 2.5 years of follow-up were evaluated to enhance their positive predictive value for asthma.

CONCLUSIONS

This national cohort study is the largest to date of the association between preterm birth and the subsequent risk of asthma, and the first study with sufficient statistical power to evaluate this risk in young adults who were born extremely preterm. The results suggest that extreme preterm birth (gestational age 23–27 weeks), but not later preterm birth, is associated with an increased risk of asthma at least into young adulthood. Additional research is needed to confirm these findings in other populations and to clarify

the biological mechanisms. Recognition of extreme prematurity as a potentially important risk factor for asthma in later life may lead to better detection and treatment in susceptible individuals throughout their life course, and will be increasingly important as larger numbers of these individuals enter adulthood.

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