Is the Association Between Low Birth Weight and Asthma Independent of Genetic and Shared Environmental Factors?

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Epidemiologic evidence linking birth weight and asthma is inconsistent. The authors examined the association between birth weight and asthma during childhood and adult life in twins. Using prospectively collected data on 21,588 like-sexed Swedish twins of known zygosity born in 1928–1952, they first conducted a cohort study to examine the risk of asthma in relation to birth weight. Next, they conducted nested co-twin control analyses among 643 dizygotic and 365 monozygotic twin pairs discordant for asthma to ascertain whether the association between birth weight and asthma could be confounded by genetic and shared environmental exposures. In the cohort analysis, birth weight of <2,500 g was associated with significantly greater risk of asthma independent of perinatal characteristics and within-twin-pair correlations. In the co-twin control analyses, birth weight of <2,500 g was significantly related to increased risk of asthma among monozygotic twins (relative risk for 2,000 g vs. 2,500 g = 1.58, 95% confidence interval: 1.06, 2.38). A negative association between birth weight and asthma, albeit not statistically significant, was also found among dizygotic twins. In conclusion, there is a negative association between birth weight and asthma in twins that is unlikely to be confounded by genetic or shared environmental factors.

asthma; birth weight; confounding factors (epidemiology); twins

Abbreviations: CI, confidence interval; SALT, Screening Across the Lifespan Twin.

The prevalence of asthma has recently increased sharply among children and adults in both developed and developing countries (1), imposing ever-growing burdens on patients’ quality of life and costs to health care systems. It is estimated that asthma currently affects 300 million people worldwide (2). The recent rises in the prevalence of asthma suggest that changes in environmental factors play an important etiologic role, and many such factors are likely to operate early in life and before birth.

Of the perinatal exposures that could be related to the risk of asthma in offspring, birth weight has been one of the most widely studied. As a general measure of fetal growth and maternal nutrition before and during pregnancy, birth weight could be related to the risk of asthma through several mechanisms, including the development of T-cell helper 1 and 2 responses, influencing risk of infections in early life, and affecting the relative size of the lungs and airways. Epidemiologic evidence linking birth weight and asthma is, however, inconsistent. While several studies found that low birth weight was related to increased risk of asthma (3–12), some others have shown null (13–18) or positive (19) associations between birth weight and the disease.

One important critique of studies that examine whether low birth weight influences risk of disease in the offspring is the extent to which the associations could be confounded by environmental or genetic factors shared within the family. This issue is very relevant in the case of asthma, because maternal asthma is a strong predictor of early- and late-onset asthma in offspring (12, 20) and could be a risk factor for low birth weight (21–23). Studies among twins offer an opportunity to examine the associations between birth weight, as an indicator of fetal growth, and the offspring’s risk independent of shared environmental or genetic factors.
Twin siblings share the same exposures to maternal factors, the intrauterine environment, early life experiences, and genes (all if monozygotic and half if dizygotic). In addition, birth weight frequently differs between twins (24), and, given that twins share gestational age, these birth weight differences represent variability in fetal growth.

Using prospectively collected information, we conducted a study among 21,588 like-sexed Swedish twins of known zygosity. Our goal was to examine the risk of asthma in relation to birth weight and to ascertain the extent to which this association could be confounded by shared (familial) genetic and environmental factors.

MATERIALS AND METHODS

Study population

The study population consisted of 37,392 like-sexed twins who were born in Sweden between 1926 and 1958 and are included in the Swedish Twin Registry (25). For the asthma study, we restricted the cohort to intact twin pairs of known zygosity (n = 32,580). Zygosity was assessed through questions on physical resemblance during childhood. This self-report was later validated with DNA markers in a subsample of 199 twin pairs and was accurate for 99% of the participants (25). In 1973, a questionnaire on health and lifestyle habits was mailed to twins from intact pairs residing in Sweden. Ninety percent of the twins of known zygosity responded to the 1973 questionnaire (25).

Outcome

We used 3 sources of information to identify participants who had ever received a diagnosis of asthma: the Screening Across the Lifespan Twin (SALT) study, the Swedish In-patient Registry, and the Swedish Total Population Registry. The SALT study was a telephone interview conducted in 1998 among 32,905 like-sexed twins registered in the Swedish Twin Registry, who were born in 1958 or earlier and were alive and residing in Sweden at the time (26). The overall response rate was 74%, and nonresponse was mostly due to refusal or inability to contact the participants. In the cohort of 32,580 twins of known zygosity for the current study, 23,545 responded to the SALT study. During the SALT study interview, participants were asked questions about their health and medical history (25), including history of asthma and age at onset of symptoms.

The In-patient Register contains data on hospital discharge diagnoses from selected parts of Sweden since 1964 and from the whole country since 1987. The principal and as many as 7 secondary diagnoses are coded according to the International Classification of Diseases, Ninth Revision from 1987 through 1996 and the International Classification of Diseases, Tenth Revision since 1997 (27). A diagnosis of asthma comprised the following codes: 493A, 493B, and 493X (Ninth Revision) and J45 and J46 (Tenth Revision). Records are identified in the registry through a unique personal identification number assigned to virtually all people residing in Sweden. By using this number, we identified inpatient diagnoses for 25,927 of the 32,580 twins of known zygosity under consideration. Finally, we searched for the participating twins in the Swedish Total Population Registry, which contains information on vital status and causes of death of Swedish residents (28). Primary and several secondary causes of death are coded according to the International Classification of Diseases. With the use of the unique identification number, we identified 2,831 deaths by 2003 among the twins of known zygosity in this cohort.

We assigned a diagnosis of asthma if at least one of the following criteria was present: 1) the participant responded yes in the SALT study interview to the question, Have you been told that you have or have had asthma by a doctor at a doctor’s office or hospital? (n = 1,526); 2) the participant had asthma as one of the in-patient diagnoses, primary or secondary, according to the International Classification of Diseases codes (n = 541); or 3) asthma was a cause of death (n = 20). Eighty-five percent of the twins who appeared as asthmatics in the In-patient or Total Population Registries had responded affirmatively to the SALT study question on physician-diagnosed asthma.

Exposures

We obtained information on maternal and birth characteristics from original medical birth records kept at local delivery archives throughout Sweden. The law requires recording of such characteristics, usually by the attending midwife, and preservation of the records. We ensured correct birth identification of each twin within a pair by restricting the analysis to twin pairs who were both baptized and named at birth or, among SALT study participants, those who agreed on birth order. Agreement on birth order between the birth records and SALT study is 95% for twins who agreed on birth order. Medical birth records with correct identification of individual twins were obtained for 23,711 (73%) of the 32,580 like-sexed twins of known zygosity. Of these twins, 23,600 had valid birth weight information, and 22,586 also had information on asthma diagnosis. We further excluded 998 subjects from incomplete twin pairs, for a final sample size of 21,588.

Gestational age was defined according to the date of the last menstrual period. Parental socioeconomic status was classified according to occupation, following the categories recommended by Statistics Sweden (29). The highest socioeconomic status of the parents was used to define socioeconomic status at birth.

Data analyses

Cohort analysis. We first examined the associations between birth weight or gestational age and asthma in the twin cohort, including all 21,588 participants. We fitted restricted cubic splines (30) to estimate relative risks and 95% confidence intervals for asthma by birth weight or gestational age as continuous variables. Spline variables for birth weight or gestational age were introduced as covariates into binomial regression models in which asthma was the outcome (PROC GENMOD; SAS Institute, Inc., 2009;169:1337–1343).
Cary, North Carolina). We assumed a log-link function and specified an exchangeable correlation matrix in the models to account for within-twin-pair correlations. We fitted multivariate models to obtain estimates adjusted for participants’ sex and year of birth and their mothers’ age, parity, and socioeconomic status at delivery. We conducted supplemental analysis to examine the associations between birth weight categories and time-to-onset of asthma in a subgroup of participants who reported age at initiation of symptoms. We used Kaplan-Meier plots and fitted a Cox proportional hazards model.

Co-twin control analyses. To examine the associations between birth weight and asthma independent of common genetic and shared environmental influences, we used a nested co-twin control design (31). These analyses were restricted to twins discordant for asthma. Within each pair, the healthy co-twin was considered the matched control for the case.

We estimated odds ratios and 95% confidence intervals with the use of conditional logistic regression models in which case status was the outcome and predictors included spline variables for birth weight. The models were fitted separately for dizygotic (n = 1,286) and monozygotic (n = 730) twins. The matched nature of this design minimizes confounding by shared intrauterine exposures, maternal factors, and general childhood and adolescent environment, since 97% of the twins reported that they lived with their co-twin until 15 years of age. If the association estimated in the co-twin analyses is smaller than that in the cohort design, the latter is probably confounded by these shared exposures. In addition, since dizygotic and monozygotic twins share 50% and 100% of their segregating genes, respectively, the co-twin control design also allows assessment of the extent to which the association between birth weight and asthma could be confounded by genetic factors. Genetic factors are fully controlled for among monozygotic twins; thus, a smaller association among monozygotic than among dizygotic twins could indicate that the latter is confounded by genetic factors. If the associations from the co-twin control design are similar between monozygotic and dizygotic twins but smaller than those from the cohort design, the latter may be confounded by shared environmental factors.

We deliberately avoided adjustment for twin characteristics measured in adulthood, including body mass index, height, and smoking. These variables could be in the causal pathway between fetal growth and asthma, and adjustment for them could bias the estimated association (32). In addition, these variables would have been measured after the outcome among twins with childhood-onset asthma.

The study was approved by the research ethics committee of the Karolinska Institutet, Stockholm, Sweden.

RESULTS

The estimated cumulative incidence of physician-diagnosed asthma was 5.8% and was significantly greater in women than men (Table 1). In univariate analyses, there was a U-shaped association between gestational age at birth and risk of asthma; twins born preterm or after 41 weeks had a significantly higher incidence of asthma compared with those born at term (Table 1). Birth weight, birth length, and head circumference were each inversely, linearly related to the risk of asthma.

We further examined the associations between indicators of fetal growth and asthma by using a cohort design in which we accounted for correlation within twin pairs. Birth weight was negatively associated with the risk of asthma, independent of gestational age, sex, year of birth, or maternal age, parity, or socioeconomic status (Figure 1A). Birth weights of <2,500 g were linearly related to a significantly higher risk of asthma. For example, compared with that for babies with a birth weight of 2,500 g, the adjusted risks of asthma for those weighing 2,000 g and 1,500 g were 21% (95% confidence interval (CI): 5, 40) and 48% (95% CI: 7, 105) higher, respectively (Figure 1A). Although, in univariate analysis, the risk of asthma appeared to be higher for twins born preterm or postterm compared with those born at term, the association was attenuated and became nonsignificant after adjustment for birth weight, sex, and other perinatal characteristics (Figure 1B).

Next, we assessed the association between birth weight and asthma in co-twin control analyses. Among monozygotic twins, birth weights of <2,500 g were related to increased risks of asthma (Figure 2A). Compared with the risk associated with birth weights of 2,500 g, the relative risks for babies weighing 2,000 g and 1,500 g were 1.58 (95% CI: 1.06, 2.38) and 2.75 (95% CI: 1.04, 7.27), respectively. Birth weight was also negatively related to the risk of asthma among dizygotic twins, but the association was not statistically significant (Figure 2B).

Finally, we conducted supplemental analyses to examine the risk of time to onset of asthma in relation to birth weight for 804 (62%) of 1,296 twins with asthma who also reported age at initiation of symptoms. In univariate analyses, a birth weight of <2,000 g was related to a 50% increased risk of asthma (95% CI: 20, 88) compared with a birth weight of 2,500–2,999 g (Figure 3). The hazard ratios for birth weight categories 2,000–2,499 g, 3,000–3,499 g, and ≥3,500 g were 1.18 (95% CI: 1.00, 1.41), 0.92 (95% CI: 0.75, 1.13), and 1.06 (95% CI: 0.75, 1.48), respectively. After adjustment for sex, gestational age, and characteristics at the time of birth, including maternal age and parity, year, and parental socioeconomic status, the hazard ratio for the <2,000-g group compared with the 2,500–2,999-g group was 1.34 (95% CI: 1.02, 1.76), whereas the hazard ratios for the other categories remained essentially unchanged (data not shown). The survival function was not constant over time in the <2,000-g group (P for interaction with time = 0.05), and the Kaplan-Meier plot (Figure 1) suggested that low birth weight was associated with adult-onset asthma rather than with childhood asthma. We therefore examined the association between very low birth weight and adult-onset asthma following the co-twin control strategy. For 160 monozygotic twin pairs discordant for adult-onset asthma, the odds ratio for a birth weight of <2,000 g versus ≥2,000 g was 1.67 (95% CI: 0.73, 3.81). For 244 discordant dizygotic twin pairs, the corresponding odds ratio was 1.50 (95% CI: 0.72, 3.11).
DISCUSSION

Lower birth weight was associated with increased risk of asthma in this cohort study of twins. Similar associations were found among monozygotic and dizygotic twin pairs. In the cohort study, gestational age was not related to increased risk of asthma after we adjusted for birth weight. Overall, these results indicate that an association between low birth weight and risk of asthma is probably not confounded by shared environmental or genetic factors.

Our finding of an association between low birth weight and the risk of asthma is consistent with a number of previous reports. Studies in the United States (3, 5, 6, 9, 11, 33–36), Canada (7), the United Kingdom (37, 38), the Netherlands (10), Finland (8, 12, 39), Israel (4), and Australia (40, 41) found that low birth weight was related to increased risk of self-reported asthma (3, 39), physician-diagnosed asthma (4, 6–9, 11, 33–36, 40, 41), and wheezing (5, 10, 37, 38, 40) during childhood or adolescence. In several other studies, however, a significant association between low birth weight and asthma was not found (13–18, 42–45), and, in at least one study (19), low birth weight was related to decreased risk of reported asthma in children. Some potential explanations for these inconsistencies across studies include varying statistical power, use of different definitions of low birth weight and asthma, differing variability in birth weight distributions between study populations, use of diverse follow-up periods for asthma, lack of control for confounding by gestational age at birth and maternal smoking or socioeconomic status, or control for variables that might be in the causal pathway between birth weight and asthma.

Our study of twins offers a major advantage because the associations in the co-twin control analyses were not confounded by unmeasured shared environmental or socioeconomic influences, and, among monozygotic twins, they were also independent of common genetic factors. In addition, differences in birth weight within twin pairs should...
reflect fetal growth. Another advantage is that information on perinatal and parental sociodemographic characteristics was retrieved from original birth records; thus, recall bias regarding the exposures is not a source of bias. Finally, our sample size was large in comparison with a previous study of Finnish adolescents in which the associations between birth weight and physician-diagnosed asthma were examined by using a co-twin control framework (16). In the Finnish study, birth weight was lower among cases compared with controls in 32 monozygotic twin pairs, whereas, among 101 dizygotic twin pairs, the birth weight of cases was slightly higher. These differences were not statistically significant.

A recent meta-analysis of 9 studies indicated an apparent increased risk of asthma associated with high birth weight (46). The definitions of high birth weight varied substantially across studies. A more recent cohort study in the United States found no associations between high birth weight (≥4,000 g) and physician-diagnosed asthma or wheezing in infants over the first 2 years of life (45). Similarly, we did not find significant associations between high birth weight and asthma in our cohort or co-twin control analyses; there were few participants of high birth weight in our study of twins, and statistical power to examine this question was limited. It remains to be determined whether there is a causal association between high birth weight and asthma.

Preterm delivery could be related to increased risk of asthma, according to some studies (12, 47). This was not

![Figure 1](image1.png)

**Figure 1.** Adjusted relative risks of asthma by A) birth weight and B) gestational age for Swedish twins born in 1928–1952. The solid curves represent the relative risk (with 2,500 g as the reference) and the dashed lines the 95% confidence intervals. Estimates were obtained from a binomial regression model with asthma as the outcome and covariates that included restricted cubic spline terms for birth weight and gestational age; the twin's sex and year of birth; and maternal age, parity, and socioeconomic status at delivery. Only observations for which data were complete were included (n = 15,482).

![Figure 2](image2.png)

**Figure 2.** Adjusted odds ratios of asthma by birth weight among A) monozygotic (n = 730) and B) dizygotic (n = 1,286) Swedish twins discordant for asthma and born in 1928–1952. The solid curves represent the odds ratios (with 2,500 g as the reference) and the dashed lines the 95% confidence intervals. Estimates were obtained from conditional logistic regression models with case status (asthma) as the outcome and restricted cubic spline terms for birth weight as covariates. Twin pairs were matched for shared environmental and genetic factors.

![Figure 3](image3.png)

**Figure 3.** Kaplan-Meier plot of the cumulative incidence of asthma in relation to birth weight categories among Swedish twins born in 1928–1952.
the case in our cohort analysis of twins; preterm birth was not related to asthma after we adjusted for birth weight. Most previous studies considered the risk of asthma during childhood only, whereas we examined asthma incidence over adult life as well. It is possible that the association between gestational age and asthma differs for child onset and adult onset. The co-twin control framework does not permit examining the association between gestational age and asthma because cases and controls are fully matched for this factor.

Few studies have previously examined the association between birth weight and asthma at different ages. In the 1970 British Cohort Study, low birth weight was associated with asthma by age 5 years but not by age 16 years (37). In northern Finland, a low ponderal index was not predictive of physician-diagnosed asthma by age 31 years, although it was associated with a higher risk of atopy (17). Our supplemental analyses of time to onset of asthma suggested that low birth weight was more strongly related to adult-onset asthma than to childhood asthma. While prepubertal asthma occurs more frequently in boys, adult-onset asthma is more common in women than men (48, 49). Whether mechanisms mediating an impact of low birth weight on asthma could be related to alterations in sex hormone pathways throughout life is speculative. This finding requires confirmation in future studies.

We used a composite definition of physician-diagnosed asthma that included self-report or the presence of asthma diagnoses in inpatient and death registries. Although it was not possible to formally estimate agreement between different sources because asthma is not always a cause of hospitalization or death, and the sources were complementary, we noted that 85% of participants for whom asthma was listed in the registries had also reported that they had been diagnosed with asthma by a physician. This finding can be taken as an indication of the validity of self-response, at least for cases for whom asthma was a hospital discharge diagnosis or a cause of death.

The generalizability of results from twin studies may be questionable. Twins are in general more growth restricted than singletons and they may differ in prenatal environment and upbringing. With asthma, there is no clear evidence that incidence varies between singletons and twins. The rates of hospital admission for asthma (50) or medical diagnosis of asthma at age 18 years (51) have been found to be lower in twins compared with singletons, but these differences have been attributed to a protective effect of large families against allergies rather than to differences in birth weight. Other studies have found comparable rates of asthma in twins and singletons (52, 53). Our finding of a negative association between birth weight and asthma in the twin cohort had also been reported in several previous studies of singletons.

In conclusion, low birth weight is associated with increased risk of asthma in twins, and this association does not appear to be confounded by shared environmental or genetic influences. Whether the mechanisms to explain this association are related to early programming of immune responses and airway inflammation or to reduced lung growth and airway caliper require future examination.

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