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Original Contribution

Body Mass Index May Modify Asthma Prevalence Among Low-Birth-Weight Children

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Childhood asthma, a growing health concern, has been associated with low birth weight and elevated body mass index. This study tested the hypothesis that overweight and obese adolescents with a history of low birth weight are at even greater risk of developing asthma. A cohort of 75,871 junior high school students was screened for asthma during 1995–1996 in Taiwan. Birth weight and estimated gestational age were obtained from the birth registry. Logistic regression and simple regression analyses were adjusted for confounding variables. Asthma was more prevalent in those with birth weights below 3,000 g and higher adolescent body mass indexes. Furthermore, those with both characteristics were consistently most likely to have asthma. Whether the asthma diagnosis among low-birth-weight subjects was assigned by physicians or medical questionnaire, the risks were elevated for both overweight (physician diagnosis: odds ratio = 1.41; medical questionnaire: odds ratio = 1.25) and obese (physician diagnosis: odds ratio = 1.38; medical questionnaire: odds ratio = 1.47) boys as well as overweight (physician diagnosis: odds ratio = 1.63; medical questionnaire: odds ratio = 1.30) and obese (physician diagnosis: odds ratio = 1.44; medical questionnaire: odds ratio = 1.32) girls ($P < 0.05$). Low birth weight predisposes one to develop asthma, and excess body mass amplifies the risk. A sex difference was observed. This study suggests that prenatal care and nutritional counseling could reduce asthma prevalence.

adolescent; asthma; birth weight; body mass index; obesity

Abbreviations: AGA, appropriate for gestational age; FEF25%–75%, forced expiratory flow between 25% and 75% of vital capacity; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; LGA, large for gestational age; SGA, small for gestational age.

Asthma is an increasingly common respiratory disorder characterized by both chronic airway hyperreactivity and inflammation. The pathology that can be intrinsic and/or extrinsic in origin includes prominent roles for mast cells, eosinophils, and T lymphocytes (1). Although the acute symptoms of asthma—wheezing, breathlessness, chest tightness, and cough—are generally treatable, the prevalence and cost of the disorder have increased progressively for several decades. Asthma, especially in childhood and adolescence, is an important public health issue with an increased prevalence observed worldwide (2–5). The prevalence of childhood asthma in Taiwan increased 15-fold from 1.3% to 19.0% during the 30-year period spanning from 1974 to 2003 and appears to be continuing upward (6, 7). The National Center for Health Statistics in the United States estimated the US asthma prevalence at 8.2% for 2009 (8). The prevalence was highest in adolescents and young adults and particularly among the economically disadvantaged. Not surprisingly, those under 18 years of age were also the greatest consumers of asthma-related medical services.

A number of factors have been proposed as useful for predicting asthma risk. Understandably, the most prominent candidates are associated with inflammatory processes, allergen exposure, and/or the subjective and quantitative metrics of respiratory performance. Inflammation is a key component of clinical asthma. Granulocytic infiltration is a common

Table 1. Comparison of Demographic Characteristics and Lung Function Between Boys and Girls in an Asthma Survey of Taiwanese Junior High School Students Screened During 1995–1996

	Boys (n = 38,155)			Girls (n = 37,026)		
	No.	%	Mean (SD)	No.	%	Mean (SD)
At birth						
Birth weight, g						
<3,000	6,465	16.9		8,497	22.9	
3,000–4,000	28,448	74.6		26,569	71.8	
>4,000	3,242	8.5		1,960	5.3	
Gestational age, weeks						
<37	875	2.3		790	2.1	
37–40	34,863	91.4		33,652	90.9	
>40	2,417	6.3		2,584	7.0	
Birth percentile						
Small for gestational age	3,629	9.5		4,267	11.5	
Appropriate for gestational age	31,436	82.4		28,431	76.8	
Large for gestational age	3,090	8.1		4,328	11.7	
During school age						
Height, cm						
<150	2,536	6.6		3,362	3.6	
150–165	18,016	47.2		30,691	82.9	
>165	17,603	46.1		2,973	8.0	
Weight, kg						
<40	2,826	7.4		2,726	7.4	
40–60	23,772	62.3		29,012	78.4	
>60	11,557	30.3		5,288	14.3	
Body mass index[a]						
<17	4,345	11.4		3,904	10.5	
17–20	20,192	52.9		19,987	54.0	
21–23	5,770	15.1		6,435	17.4	
>23	7,848	20.6		6,700	18.1	
Age, years						
<13	3,409	8.9		3,296	8.9	
13	13,111	34.4		12,442	33.6	
14	12,789	33.5		12,523	33.8	
≥15	8,846	23.2		8,765	23.7	

Table continues

finding in asthma, with increased circulating and bronchial eosinophils present in approximately one half of cases (9). The proteins associated with eosinophils have been suggested for tracking the efficacy of corticosteroid therapy in childhood asthma (10, 11).

Studies have related low birth weight and/or lower gestational ages to subsequent asthma in childhood (12–16) and adolescence (17). A twin study showed that low birth weight is associated with adult-onset asthma, and the analyses suggested that the findings were unlikely to be confounded by genetic or shared environmental factors (18). Excess body mass has also been associated with the development of asthma during childhood (19, 20) and adolescence (21, 22). Thus, both lower birth weight and a higher body mass index in adult life have been independently associated with increased asthma risk in young adults (23).

Animal models and epidemiologic studies have shown that low-birth-weight infants gaining weight rapidly may have a higher relative body fat mass (24–26). The intrauterine adjustments associated with low birth weight may promote higher adiposity in later life stages (25). Furthermore, low birth weight with its attendant infant catch-up growth is

Table 1. Continued

	Boys (n = 38,155)			Girls (n = 37,026)		
	No.	%	Mean (SD)	No.	%	Mean (SD)
Family characteristics						
Paternal education, years						
≤6	13,785	36.1		13,622	36.8	
7–9	8,205	21.9		7,921	21.4	
10–12	10,536	27.6		10,155	27.4	
≥13	5,629	14.8		5,328	14.4	
No. of smokers at home						
0	15,107	39.6		14,662	39.2	
1	16,695	43.8		16,730	45.2	
>1	6,353	16.7		5,634	15.2	
Lung function tests						
FEV_1, mL			3,167 (637)			2,538 (498)
FVC, mL			3,473 (669)			2,749 (470)
FEV_1/FVC ratio			0.91 (0.09)			0.92 (0.11)
FEF25%–75%, mL/second			4,071 (1,107)			3,562 (948)
PEF, mL/second			6,413 (1,833)			5,167 (1,580)

Abbreviations: FEF25%–75%, forced expiratory flow between 25% and 75% of vital capacity; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; PEF, peak expiratory flow; SD, standard deviation.
[a] Body mass index: weight (kg)/height $(m)^2$.

associated with a significant risk of adult obesity, inflammation, and pulmonary dysfunction (27–29), which could increase the risk of developing respiratory diseases, especially asthma.

Children, 3 years of age, with lower birth weight or higher body mass index are at an increased risk of chronic respiratory illness. Children who are initially in the lowest birth weight tertile but are later in the highest weight tertile may have a higher risk of chronic respiratory illness, compared with those who remained in the middle tertile (30). The objective of this study was to examine whether asthma is more prevalent in overweight and/or obese adolescents with a history of low birth weight.

MATERIALS AND METHODS

Birth cohort

The birth cohort linked 2 major databases: the Taiwan Birth Registry and a 6-month mass screening of adolescent schoolchildren for asthma and basic lung function. The Taiwan Birth Registry was established by the Ministry of the Interior in 1978 to assemble standardized information from birth certificates regarding birth date, sex, single/multiple pregnancy, gestational age, birth weight, and limited parental demographic information (31). Infants were classified by birth weight as small for gestational age (SGA, <10th percentile), appropriate for gestational age (AGA, between the 10th and 90th percentiles), and large for gestational age (LGA, >90th percentile), on the basis of nationwide singleton birth-weight percentiles by gestational age in Taiwan (32).

A 6-month mass screening was conducted to survey for adolescent asthma and to record basic lung function. The survey was conducted by the National Taiwan University and the Environmental Protection Administration in Taiwan between October 1995 and March 1996. Of the country's 1,139,452 junior high school students, 89% (n = 1,018,031) completed questionnaires that subsequently passed a computerized quality assurance screen. Students were 10–17 years of age with the majority (92%) between ages 12 and 15 (6, 33, 34). Quality control within the survey was maintained by working groups led by recognized national experts in the fields of quality assurance and quality control, clinical medicine, education and training, statistics, computing, and epidemiology. They met weekly to resolve problems associated with training, survey standards, data entry, and computing and to review results of the questionnaire survey and lung function tests.

Study population

For this study, 85,791 students were randomly selected from all participating junior high school students. Surveys with missing data were excluded, including missing birth dates (n = 4,468), gestational age (n = 1,192), birth weight (n = 385), body weight (n = 38), body height (n = 14), and parity information (n = 67). Students with lung function tests that failed to meet the American Thoracic

Society-based criteria A and B were also excluded from the study ($n = 4,259$). Following exclusions, 75,181 subjects remained in the analysis, including 38,155 boys and 37,026 girls.

Definition of asthma

Chinese language questionnaires were adapted from the International Study of Asthma and Allergies in Childhood (ISAAC) and New England Core questionnaires. Students responded to the first questionnaire, a video questionnaire, and parents completed the New England Core questionnaire. Ten teams of 25 persons conducted the surveys. To permit international comparisons, answers recorded as ''unknown'' were excluded. The diagnosis of asthma was based on answers from both parents and students. If the parent/student responses did not coincide, the more serious condition was used for analyses. This was based on the recommendation of an adolescent respiratory system-screening technical consultant. Two asthma diagnoses were considered. Physician-diagnosed asthma was defined by parental reports of the child's being diagnosed by a physician as having asthma. The questionnaire-diagnosed asthma was derived from a combination of responses from the child and his/her parents. The video questionnaire considered asthmatic symptoms including dyspnea, wheezing, exercise-induced wheezing, wheezing, or dry cough at night unassociated with a cold. Thus, classification relied on reported dyspnea and nocturnal dyspnea associated with wheezing (from the video questionnaire), reported attacks of dyspnea with wheezing (from the parental questionnaire), or physician-diagnosed asthma (reported by a parent) (33).

Lung function testing

Lung function testing was performed following the 1977 criteria of the American Thoracic Society and the 1987 American Thoracic Society Snowbird Conference. A total of 10% of participating students were randomly selected by computer for respiratory testing. The major test items were forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), the FEV_1/FVC ratio, forced expiratory flow between 25% and 75% of vital capacity (FEF25%–75%), and peak expiratory flow. Body weight and height were measured before lung function testing. Lung function was assessed with SensorMedics model 2130 computerized spirometers (SensorMedics, Yoba Linda, California).

Statistical analysis

Odds ratios and 95% confidence intervals were estimated by multiple logistic regression models for binary outcomes (asthma: yes or no) associated with birth weight, gestational age, birth percentile, current height, weight, and body mass index for both genders. Adjustments were made for the child's age, paternal education, and environmental tobacco smoke. Birth condition (birth weight and birth percentile) and body mass index for adolescent boys and girls were also associated with the prevalence of asthma. The mean and standard error were calculated by multiple regression models for continuous outcomes (lung function) related to birth weight and body mass index during adolescence for boys and girls. SAS, version 9.2, software was used in the analyses (SAS Institute, Inc., Cary, North Carolina). All of the reported P values were based on a 2-tailed assumption with an accepted statistical significance of $P < 0.05$.

RESULTS

The primary measures were concentrated around expected norms. Birth weights for the majority of subjects were between 3,000 and 4,000 g with appropriate gestational ages (37–40 weeks) and a healthy current body mass index (17–20 kg/m^2). Birth weights less than 3,000 g were more common in girls (22.9%) than boys (16.9%). SGA was also more likely among girls (11.5% vs. 9.5%). When overweight and obese students were combined, the distribution between genders was similar: 35.7% for boys and 35.5% for girls.

Parental education and environmental tobacco smoke exposure were similar between genders. For instance, in the largest educational category, 36.1% of boys and 36.8% of girls were raised in households where the parents had 6 or fewer years of education. Environmental tobacco smoke exposure was high at 60.4% for boys and 60.8% for girls.

As expected, the physically larger boys had greater lung capacities (Table 1). The mean FEV_1 was 3,167 mL for boys and 2,538 mL for girls. Also, the mean FVC was 3,473 mL for boys and 2,749 mL for girls. When normalized, however, the mean FEV_1/FVC ratio was similar, 91% for boys and 92% for girls. Again, not unexpectedly, the peak and mid expiratory flows were higher in boys (4,071 and 6,413 mL/second) than in girls (3,562 and 5,167 mL/second).

Low birth weight and SGA were associated with an increased prevalence of physician-diagnosed asthma (Table 2). In contrast, pregnancies longer than 40 weeks were also at increased risk. Among boys, birth weights below 3,000 g, SGA, and gestations beyond 40 weeks were associated with an increased prevalence of physician-diagnosed asthma, with adjusted odds ratios of 1.26, 1.21, and 1.25, respectively. For girls, the odds ratios were very similar at 1.21, 1.18, and 1.21, respectively. Higher body mass indexes were suggestive of increased likelihood of asthma throughout, but only those for girls between 21 and 23 kg/m^2 were significant with an odds ratio of 1.26.

When the questionnaire was used to identify those with asthma, the relations were less consistent (Table 2). Boys with birth weights below 3,000 g, SGA, and prematurity (<37 weeks) were more likely to have asthma with accompanying odds ratios of 1.18, 1.13, and 1.22, respectively. Similar comparisons in girls were not observed. Questionnaire-based asthma risk was, however, more closely associated with body mass in both sexes. Boys weighing more than 60 kg or having a body mass index greater than 23 kg/m^2 were at greater risk of having asthma, with odds ratios of 1.10 and 1.18, respectively. Similarly, girls greater than 60 kg in weight and those with body mass indexes between 21 and 23 kg/m^2 or greater than 23 kg/m^2 were all associated with an increased prevalence of questionnaire-diagnosed asthma and accompanying odds ratios of 1.20, 1.21, and 1.29, respectively.

Table 2. Odds Ratios of Physician- and Questionnaire-diagnosed Asthma Associated With Birth Weight, Gestational Age, Birth Percentile, Current Height, Weight, and Body Mass Index for Taiwanese Boys and Girls Screened During 1995–1996

	Physician-diagnosed Asthma						Questionnaire-diagnosed Asthma					
	Boys			Girls			Boys			Girls		
	% of Cases	OR[a]	95% CI	% of Cases	OR[a]	95% CI	% of Cases	OR[a]	95% CI	% of Cases	OR[a]	95% CI
Total	5.9			3.6			12.1			8.7		
At birth												
Birth weight, g												
<3,000	7.1	1.26	1.13, 1.41	4.3	1.21	1.13, 1.41	13.8	1.18	1.09, 1.28	9.1	1.06	0.97, 1.16
3,000–4,000	5.7	1.00	Referent	3.6	1.00	Referent	11.9	1.00	Referent	8.6	1.00	Referent
>4,000	4.9	0.89	0.76, 1.06	3.6	1.04	0.81, 1.34	10.9	0.93	0.83, 1.05	9.3	1.23	0.96, 1.32
Gestational age, weeks												
<37	7.5	1.28	0.99, 1.65	3.7	1.02	0.70, 1.48	14.7	1.22	1.01, 1.47	8.5	0.99	0.76, 1.27
37–40	5.7	1.00	Referent	3.7	1.00	Referent	12.0	1.00	Referent	8.6	1.00	Referent
>40	8.0	1.25	1.07, 1.46	5.1	1.21	1.01, 1.46	13.5	1.04	0.92, 1.18	10.3	1.12	0.98, 1.28
Birth percentile												
Small for gestational age	6.8	1.21	1.05, 1.39	4.3	1.18	1.01, 1.39	13.2	1.13	1.02, 1.25	9.3	1.09	0.89, 1.22
Appropriate for gestational age	5.8	1.00	Referent	3.8	1.00	Referent	12.1	1.00	Referent	8.7	1.00	Referent
Large for gestational age	5.3	0.91	0.77, 1.08	3.2	0.89	0.74, 1.06	11.3	0.93	0.83, 1.05	8.8	1.04	0.93, 1.17
During school age												
Height, cm												
<150	6.5	1.14	0.96, 1.35	3.6	1.03	0.85, 1.25	13.3	1.07	0.95, 1.22	8.2	0.95	0.83, 1.08
150–165	6.0	1.00	Referent	3.7	1.00	Referent	12.5	1.00	Referent	8.8	1.00	Referent
>165	5.7	0.95	0.86, 1.05	4.0	1.04	0.86, 1.26	11.6	0.94	0.88, 1.01	9.2	1.05	0.92, 1.08
Weight, kg												
<40	5.8	0.99	0.84, 1.18	3.0	0.82	0.65, 1.03	12.5	1.03	0.92, 1.17	7.4	0.85	0.73, 0.99
40–60	5.8	1.00	Referent	3.8	1.00	Referent	11.8	1.00	Referent	8.6	1.00	Referent
>60	6.0	1.01	0.92, 1.11	4.1	1.12	0.96, 1.29	12.7	1.10	1.02, 1.17	10.2	1.20	1.09, 1.33
Body mass index[b]												
<17	5.8	1.03	0.89, 1.19	2.8	0.77	0.63, 0.94	12.1	1.04	0.94, 1.16	7.2	0.85	0.74, 0.97
17–20	5.6	1.00	Referent	3.6	1.00	Referent	11.5	1.00	Referent	8.3	1.00	Referent
21–23	6.4	1.19	0.99, 1.26	4.5	1.26	1.09, 1.44	12.4	1.08	0.99, 1.18	9.9	1.21	1.10, 1.33
>23	6.2	1.07	0.96, 1.20	4.0	1.12	0.97, 1.30	13.5	1.18	1.09, 1.28	9.7	1.29	1.08, 1.31

Abbreviations: CI, confidence interval; OR, odds ratio.
[a] Adjusted for child's age, paternal education, and environmental tobacco smoke.
[b] Body mass index: weight (kg)/height $(m)^2$.

Adjusted odds ratios for the risk of physician-diagnosed and questionnaire-determined asthma by birth weight and adolescent body mass index are shown in Figure 1. Both boys and girls who were low birth weight and currently overweight or obese were consistently at a higher risk of asthma. However, a sex difference appeared. The odds ratios of asthma for boys were consistently reversely associated with birth weights regardless of body mass index levels with a narrow variation. Higher birth weight showed a trend of protection of being nonasthmatic. On the other hand, there was a much larger variation in asthmatic risks from the interaction between birth weights and body mass index levels in girls. Higher birth weight girls were consistently at a lower risk of asthma; the odds ratio was particularly lower in those with a low body mass index. However, a U-shaped association appeared in girls with body mass indexes of 21–23 kg/m^2; the odds ratios were greater in those with both low birth weights and higher birth weights: 1.63 and 1.54 by the physician diagnoses and 1.30 and 1.47 by the questionnaire reports, respectively.

Adjusted odds ratios for the risk of physician- and questionnaire-diagnosed asthma by birth percentile and adolescent weight are shown in Table 3. Those born as SGA

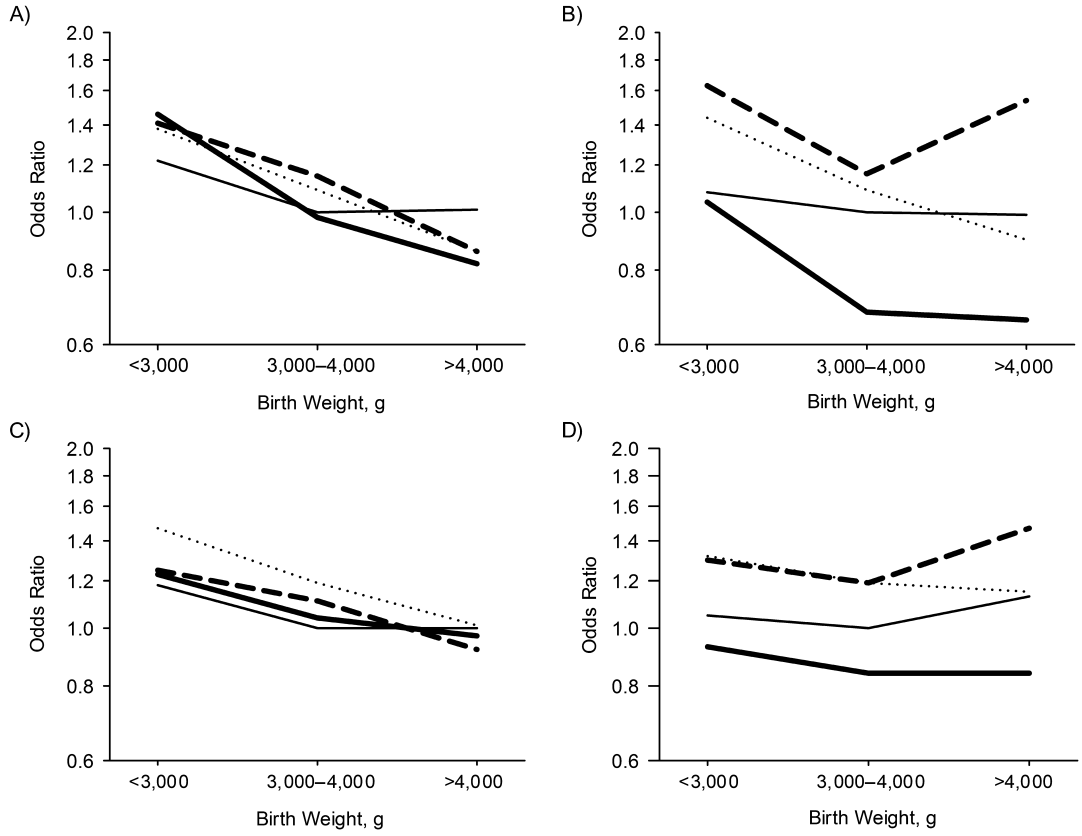

Figure 1. Multivariate odds ratios of physician (A, boys; B, girls)- and questionnaire (C, boys; D, girls)-diagnosed asthma associated with birth weight and body mass index in Taiwanese adolescents screened for asthma during 1995–1996. Odds ratios were adjusted for the child's age, paternal education, and environmental tobacco smoke. The line types (thick, thin, dashed, and dotted) represent the different body mass index groups: <17, 17–20, 21–23, and >23, respectively. Body mass index: weight (kg)/height $(m)^2$.

who later became obese had a consistently increased prevalence of physician- and questionnaire-diagnosed asthma, with respective adjusted odds ratios of 1.42 and 1.44 for boys and 1.53 and 1.37 for girls.

SGA increased the asthma likelihood for physician- and questionnaire-diagnosed asthma among normal-weight adolescent males (odds ratios = 1.25 and 1.16, respectively). This was also true for low-weight adolescent males but only for the physician-based diagnoses (odds ratio = 1.43). Females who were born SGA and were now overweight had a significantly higher questionnaire-diagnosed asthma with an adjusted odds ratio of 1.30. Males and females born at AGA who were overweight and obese in adolescence all had a significantly higher prevalence of questionnaire-based asthma with similar adjusted odds ratios for boys of 1.12 and 1.20 and for girls of 1.24 and 1.22. A similar relation was observed among AGA, body mass index, and increased prevalence of physician-diagnosed asthma except paradoxically for obese males, which did not reach significance.

Low birth weight was associated with statistically significant but minor reductions in FEV_1 and FVC across all groups (Table 4). As expected, the values were uniformly higher as the current adolescent body mass increased. When normalized to the FEV_1/FVC ratio, the low-birth-weight association resolved, and the obesity effect, though still significant, was similarly reduced in magnitude. When the more dynamic measures of lung function (FEF25%–75% and peak expiratory flow) were analyzed, the low-birth-weight effect was absent or smaller among adolescents, particularly boys currently underweight or normal weight. However, as the dynamic lung function increased with body mass, the difference between low- and high-birth-weight groups increased progressively, reaching a maximum in obese adolescents. This disadvantage associated with low birth weight and increasing body mass was exaggerated in girls.

DISCUSSION

In this national junior high school student survey, the analyses suggest that overweight or obese adolescents with a history of low weight at birth are consistently more likely to develop asthma. Similar but less consistent results were found in the SGA analyses. For those with SGA, the interaction persisted for obese adolescents throughout, but among the overweight subjects, the increased prevalence was limited

Table 3. Odds Ratios of Physician- and Questionnaire-diagnosed Asthma Associated With Birth Percentile and Body Mass Index in Adolescent Taiwanese Boys and Girls Screened During 1995–1996

Asthma Diagnosis Type by Sex and Birth Percentile	Body Mass Index[a]											
	<17			17–20			21–23			>23		
	No.	OR[b]	95% CI	No.	OR[b]	95% CI	No.	OR[b]	95% CI	No.	OR[b]	95% CI
Boys												
Physician diagnosis												
Small for gestational age	530	1.43	1.03, 2.00	1,980	1.25	1.04, 1.52	492	0.95	0.64, 1.43	623	1.42	1.05, 1.91
Appropriate for gestational age	3,586	1.00	0.86, 1.18	16,691	1.00	Referent	4,724	1.20	1.05, 1.37	6,435	1.11	0.98, 1.25
Large for gestational age	229	1.12	0.65, 1.94	1,517	1.04	0.83, 1.10	554	0.93	0.64, 1.36	790	0.79	0.56, 1.12
Questionnaire diagnosis												
Small for gestational age	530	1.16	0.95, 1.51	1,980	1.16	1.01, 1.34	492	1.09	0.82, 1.43	623	1.44	1.16, 1.80
Appropriate for gestational age	3,586	1.05	0.94, 1.18	16,691	1.00	Referent	4,724	1.12	1.02, 1.24	6,435	1.20	1.10, 1.31
Large for gestational age	229	0.99	0.66, 1.49	1,517	1.02	0.86, 1.20	554	0.87	0.66, 1.15	790	1.03	0.82, 1.28
Girls												
Physician diagnosis												
Small for gestational age	599	1.22	0.81, 1.84	2,360	1.16	0.92, 1.44	661	1.37	0.95, 1.99	647	1.53	1.07, 2.20
Appropriate for gestational age	3,020	0.73	0.58, 0.93	15,454	1.00	Referent	4,928	1.32	1.13, 1.55	5,029	1.20	1.02, 1.41
Large for gestational age	285	0.50	0.21, 1.22	2,173	1.09	0.86, 1.38	846	1.03	0.71, 1.50	1,024	0.69	0.45, 1.04
Questionnaire diagnosis												
Small for gestational age	599	1.03	0.77, 1.39	2,360	1.10	0.94, 1.28	661	1.30	1.00, 1.68	647	1.37	1.06, 1.77
Appropriate for gestational age	3,020	0.86	0.74, 1.00	15,454	1.00	Referent	4,928	1.24	1.00, 1.68	5,029	1.22	1.09, 1.36
Large for gestational age	285	0.63	0.38, 1.07	2,173	1.12	0.96, 1.31	846	1.19	0.94, 1.51	1,024	1.15	0.92, 1.43

Abbreviations: CI, confidence interval; OR, odds ratio.
[a] Body mass index: weight (kg)/height $(m)^2$.
[b] Adjusted for child's age, paternal education, and environmental tobacco smoke.

to the questionnaire-based diagnosis in girls. This inconsistent relation among SGA, subsequent body mass index, and asthma compared with the consistent effect modification observed for low birth weight and body mass index suggests that the potential influence of body mass index on asthma among low-birth-weight children will require additional research to dissect the discrepancy. Though closely related, low birth weight and SGA are not identical measures. For instance, a nonlinear association between gestational age at birth and asthma risk and also a linear association for low birth weight and asthma risk have both been observed (18). This may partially explain the higher fidelity coupling observed for low birth weight versus SGA in the current analyses. A very recent analysis reported that children with lower birth weights and higher body mass indexes have an increased risk of chronic respiratory illness at age 3 years (30), suggesting that the birth weight-associated predisposition to develop asthma may emerge in very early childhood.

Animal models have shown that low-birth-weight sheep that gain weight rapidly may have a higher relative body fat mass (24). Epidemiologic studies have reported findings consistent with those from these animal studies (25, 26). An analysis of adult obesity in England, Scotland, and Wales found a direct inverse association between birth weight and adult abdominal obesity (26). An increased body mass index appears to up-regulate inflammatory mechanisms (35), and obesity is known to increase inflammatory reactivity, for instance, to airborne particulates (36, 37). Thus, the inflammatory process and the resulting changes in airway structure and reactivity could represent the mechanistic link among low birth weight, obesity, and the risk of acquiring asthma (38). The increasing airflow limitation gradually becomes pathological (39). The current analyses indicate that adolescents born with low body weight have mild reductions in lung capacity and dynamic lung function that are exaggerated by obesity. The results were consistent with the observation

Table 4. Mean (Standard Error) Lung Function[a] Measured by Birth Weight and Body Mass Index for Adolescent Taiwanese Boys and Girls Screened During 1995–1996

Lung Function	Boys' Body Mass Index[b]				Girls' Body Mass Index			
	<17	17–20	21–23	>23	<17	17–20	21–23	>23
FEV_1, mL								
Birth weight, g								
<3,000	2,871 (16.46)	3,108 (8.56)	3,263 (16.90)	3,283 (14.62)	2,285 (13.83)	2,467 (6.70)	2,570 (12.37)	2,651 (12.59)
3,000–4,000	2,890 (9.05)	3,129 (4.08)	3,299 (7.66)	3,333 (6.61)	2,328 (8.92)	2,509 (3.83)	2,627 (6.71)	2,710 (6.57)
>4,000	2,889 (33.06)	3,151 (12.53)	3,345 (21.14)	3,380 (17.42)	2,347 (40.18)	2,546 (14.88)	2,694 (23.32)	2,780 (20.65)
$P_{difference}$[c]	<0.0001				<0.0001			
FVC, mL								
Birth weight, g								
<3,000	3,108 (16.46)	3,388 (8.55)	3,618 (16.88)	3,683 (14.62)	2,459 (12.59)	2,669 (6.10)	2,791 (11.27)	2,912 (11.46)
3,000–4,000	3,134 (9.05)	3,410 (4.08)	3,615 (7.66)	3,720 (6.60)	2,496 (8.12)	2,706 (3.49)	2,845 (6.11)	2,971 (5.98)
>4,000	3,147 (32.97)	3,441 (12.53)	3,684 (21.13)	3,780 (17.40)	2,572 (36.60)	2,742 (13.54)	2,904 (21.24)	3,032 (18.80)
$P_{difference}$[c]	<0.0001				<0.0001			
FEV_1/FVC ratio								
Birth weight, g								
<3,000	0.924 (0.003)	0.917 (0.002)	0.904 (0.003)	0.895 (0.003)	0.928 (0.003)	0.924 (0.002)	0.922 (0.003)	0.913 (0.003)
3,000–4,000	0.925 (0.002)	0.919 (0.001)	0.913 (0.001)	0.897 (0.001)	0.932 (0.002)	0.927 (0.001)	0.925 (0.002)	0.914 (0.002)
>4,000	0.919 (0.006)	0.915 (0.002)	0.908 (0.004)	0.897 (0.003)	0.914 (0.010)	0.928 (0.004)	0.931 (0.006)	0.919 (0.005)
$P_{difference}$[c]	<0.0001				<0.0001			
FEF25%–75%, mL/second								
Birth weight, g								
<3,000	3,760 (31.53)	4,005 (16.38)	4,128 (32.35)	4,049 (27.99)	3,332 (27.83)	3,480 (13.49)	3,588 (24.88)	3,546 (25.33)
3,000–4,000	3,792 (17.34)	4,077 (7.82)	4,203 (14.67)	4,164 (12.65)	3,397 (17.94)	3,547 (7.70)	3,645 (13.50)	3,704 (13.21)
>4,000	3,772 (63.17)	4,094 (24.00)	4,248 (40.48)	4,197 (33.33)	3,349 (80.87)	3,630 (29.91)	3,714 (46.93)	3,774 (41.55)
$P_{difference}$[c]	<0.0001				<0.0001			
PEF, mL/second								
Birth weight, g								
<3,000	5,855 (53.93)	6,254 (28.02)	6,635 (55.33)	6,600 (47.88)	4,751 (46.69)	5,006 (22.63)	5,247 (41.75)	5,355 (42.50)
3,000–4,000	5,923 (29.65)	6,354 (13.37)	6,642 (25.09)	6,715 (21.63)	4,818 (30.10)	5,098 (12.92)	5,350 (22.65)	5,497 (22.17)
>4,000	5,822 (108.05)	6,376 (41.05)	6,733 (69.24)	6,869 (57.02)	4,815 (135.69)	5,213 (50.19)	5,451 (78.74)	5,554 (69.72)
$P_{difference}$[c]	<0.0001				<0.0001			

Abbreviations: FEF25%–75%, forced expiratory flow between 25% and 75% of vital capacity; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; PEF, peak expiratory flow.

[a] Adjusted for child's age and child's height.

[b] Body mass index: weight (kg)/height $(m)^2$.

[c] The *P* value tested for any difference in birth weight and body mass index matrices.

in other studies that both low birth weight and obesity are associated with impaired lung function (40, 41). Thus, a smaller size at birth may precipitate an accelerated early weight gain and higher adipose fraction that then predispose one to reduced lung function (29).

The strength of the current study derives from the large representative, national sample that should provide an unbiased estimation of risk. This study is the first to address the interaction among low birth weight, adolescent body mass, and the prevalence of asthma. Retarded fetal development and the subsequent overgrowth appear to be broadly related to an increased risk of asthma and atopy. Intrauterine programming of the developing respiratory and immune systems and their subsequent interaction with accumulating fat mass seem to be an attractive hypothesis (23, 30, 42, 43).

The current analyses are consistent with previously reported associations between increased asthma risk and low birth weight (12–18, 23, 30), SGA (44), and obesity (19–23, 30). Low birth weight and being overweight in adolescence are related to poorer lung function. The low-birth-weight individuals who were obese in adolescence had the most adverse effects on lung function. Normal-weight babies who became overweight and obese during adolescence were at increased risk of developing impaired lung function and asthma. Both FEV_1 and FVC declined as adolescent body mass index increased. High birth weights were also associated with increased asthma for overweight adolescence girls. Although the odds ratios were high in both diagnostic cohorts, the association was significant only for the questionnaire-based diagnoses. The failure to achieve significance in the physician-based diagnostic cohort may represent a systematic underestimation within that grouping (33). Increased fat mass seems to be a likely contributor (43), but the causal association between high birth weight and asthma warrants further study (18).

The obesity and asthma relation may be different between boys and girls (45–47). A low birth weight–asthma relation has been proposed (48); the potential sex difference remains an issue for further studies. This study did find a sex difference regarding the interaction among low birth weight, adolescent obesity, and asthma. Low birth weight was a problem for boys regardless of body mass index but was an issue only for higher body mass index girls. The effect modification by body mass index and the apparent sex difference are important and, thus, will require additional study.

There are 2 key limitations in the analysis: 1) both asthma and obesity/overweight were cross-sectional measures, and 2) there are no specific measures of prenatal environmental tobacco smoke exposure. The cross-sectional character of the analyses makes it impossible to determine whether obesity promotes the emergence of asthma in low-birth-weight children, helps to maintain it, or actually exaggerates it. One must also consider that the constraints on physical activity imposed by asthma may promote inactivity and weight gain. Prior work has suggested that prenatal maternal smoking (or prenatal environmental tobacco smoke exposure) is related to low birth weight and SGA (48–50). Low birth weight and/or SGA might, in fact, serve as an index outcome of prenatal maternal smoking (or prenatal environmental tobacco smoke exposure). In the current analyses, the questionnaire only identified the number of smokers in the home and did not specifically differentiate between pre- and postnatal exposure or the degree of exposure.

In conclusion, our analysis suggests that low birth weight predisposes one to develop asthma, potentially as a result of early life programming. An elevated body mass index in adolescents is associated with a gradual increase in the odds ratio for asthma in the low-birth-weight cohort compared with their adolescent normal-weight counterparts. Asthma odds ratios were also higher in the low-birth-weight cohort among underweight and normal-weight adolescent boys but not so for girls. Individuals with low birth weight who later become overweight and obese adolescents have reduced lung function and the highest prevalence of asthma. These findings strongly support the need for additional analyses and for the institution of early nutritional interventions to preempt permanent airway changes.

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