



Fetal Growth, Obesity, and Atopic Disorders in Adolescence: a Retrospective Birth Cohort Study

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Abstract

Background: Developmental status at birth and subsequent obesity have been implicated in the development of childhood atopic dermatitis (AD) and allergic rhinitis (AR).

Methods: The current study analysed the cohort data of 74 688 junior high school students from a national retrospective birth cohort study in Taiwan. A random 10% sample was selected from singleton livebirths with complete data on the analytical variables of interest. Atopic disorders, including AD and AR, were assessed by questionnaires (International Study of Asthma and Allergies in Childhood). Logistic regression analyses were applied with adjustments for related risk factors.

Results: Among subjects mainly 13–15 years of age, the estimated prevalence was 7.6% for AD and 22.4% for AR. While the role of fetal growth in allergic disorders was less evident, the risk of developing AD and AR were both influenced by a combination of fetal growth status and adolescent body mass index (BMI). Compared with those with normal fetal growth and school-aged BMI, the risk of developing AD increased 64% among adolescents with both restricted fetal growth and high BMI (odds ratio 1.64, 95% confidence interval 1.37, 1.97). The risk for this combination was higher than that for either restricted fetal growth or high BMI alone. Nevertheless, the overall interaction between BMI and fetal growth status on atopic disorders did not reach statistical significance.

Conclusions: Excessive weight gain could be an important risk factor related to developing atopic dermatitis and allergic rhinitis during adolescence, especially among infants born small for gestational age.

Keywords: allergic rhinitis, atopic dermatitis, body mass index, obesity, small for gestational age.

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Atopic disorders represent a significant public health issue worldwide.¹ Atopic dermatitis (AD) and allergic rhinitis (AR) both appear to be increasing among adolescents in Taiwan.^{2,3}

Fetal growth restriction is commonly attributed to an adverse prenatal environment.⁴ These individuals are described as small for gestational age (SGA) defined as fetal weight below the 10th percentile for gestational age. While most clinical research has focused on the immediate neonatal consequences of SGA, newer findings suggest that SGA adversely affects postnatal health outcomes into adulthood.

These observations provide support for the 'developmental origins of health and disease hypothesis'.⁵ Two twin studies in Denmark and Sweden provided meaningful evidence and supported the hypothesis.^{6,7}

The consequences of fetal growth restriction are believed to include atopic disorders, despite some conflicting evidence in younger children. The development of atopic conditions later in life has been attributed in part to differences in the late gestational programming of T cells in malnourished fetuses.⁸ The factors determining the subsequent expression of AD and AR remain unclear,^{9–11} but some may result from childhood risk factors that exaggerate or moderate the prenatal influences. Several clues suggest that excess body mass is an important co-factor. A positive association between body mass index (BMI) and AD has been reported in children.^{12–14} Similar findings were found for obesity, waist circumference, and AR.^{15,16} Silverberg *et al.* reported a significant temporal association between obesity in the first 2 years of life and AD symptoms, suggesting again a relationship between BMI and early life programming.¹² An extended follow-up of the International Study of Asthma and Allergies in Childhood (ISAAC) in Germany on participants aged 16–18 years identified an association between increased BMI and rhinitis but not the other atopic disorders.¹⁷ Thus, the current study was designed to assess whether fetal growth status moderates the risk of adolescent AD and/or AR associated with excess weight gain. The design was constructed to address three key questions in a large national sample: (i) Is fetal growth restriction associated with atopic disorders? (ii) Is adolescent obesity associated with atopic disorders? And (iii) does fetal growth restriction show stronger associations with atopic disorders in adolescents with obesity?

Methods

Study population

The Taiwan Environmental Protection Administration (TEPA) from October 1995 to March 1996 conducted a national survey for allergic diseases among 1 139 452 junior high students by stratified systematic sampling. The sampling frame and quality control had been reported in details elsewhere.¹⁸ In brief, completed questionnaires were validated with the use of a computerised quality assurance programme resulting in an effective response rate of 89 per cent or 1 018 031

students (Figure 1). Of those, 85 604 students (84.1%) completed the personal interview, and 82 393 remained in the cohort after completing the birth registration linkage. After excluding multi-births and missing or incomplete data, a total of 74 688 subjects were included in the final analysis. There were no significant demographic differences between the non-participants and the participants, including maternal age, maternal history of atopy, gender, and parity (data not shown).

Ethics statement

This study has been reviewed and approved by the Taiwan Environmental Protection Administration, the Institutional Review Board at National Taiwan University with written standard procedure and protocol for verbal consent of children and Ethics Committee approval. Institutional Review Board written consent was not required in Taiwan during 1995–96; thus verbal consent from children's parents was obtained. Individual anonymity was maintained throughout study process.

Collection of demographic data and case definition

Information about birthweight and gestational age were acquired from the national birth registry. Birthweight was also reported by parents based on hospital records and formal certificates attested to by physicians. Fetal growth was categorised as: large for gestational age (fetal weights: > 90th percentile, LGA), appropriate for gestational age (fetal weights: 10–90th percentile, AGA), and small for gestational age (fetal weights < 10th percentile, SGA).¹⁹ Age, (current) body weight, and height were recorded at the time they were recruited into the cohort, and BMI was calculated as body weight (kg) divided by the square of body length (m). Students/parents responded to the standard questionnaire of ISAAC.¹⁸ Cases of AD were defined through the questions: 'Has your child ever had AD diagnosed by a physician?' and 'Has your child ever had recurrent itchy rash for at least 6 consecutive half-month periods over elbows, knees, face, wrists, neck, preauricular and eyebrow areas?' Since sleep disturbances due to skin irritation are subjective measures of AD severity, the answers to the following ISAAC questions were noted: 'In the last 12 months, how often has your child been kept awake at night by the itchy rash?' Cases of AR were defined through the

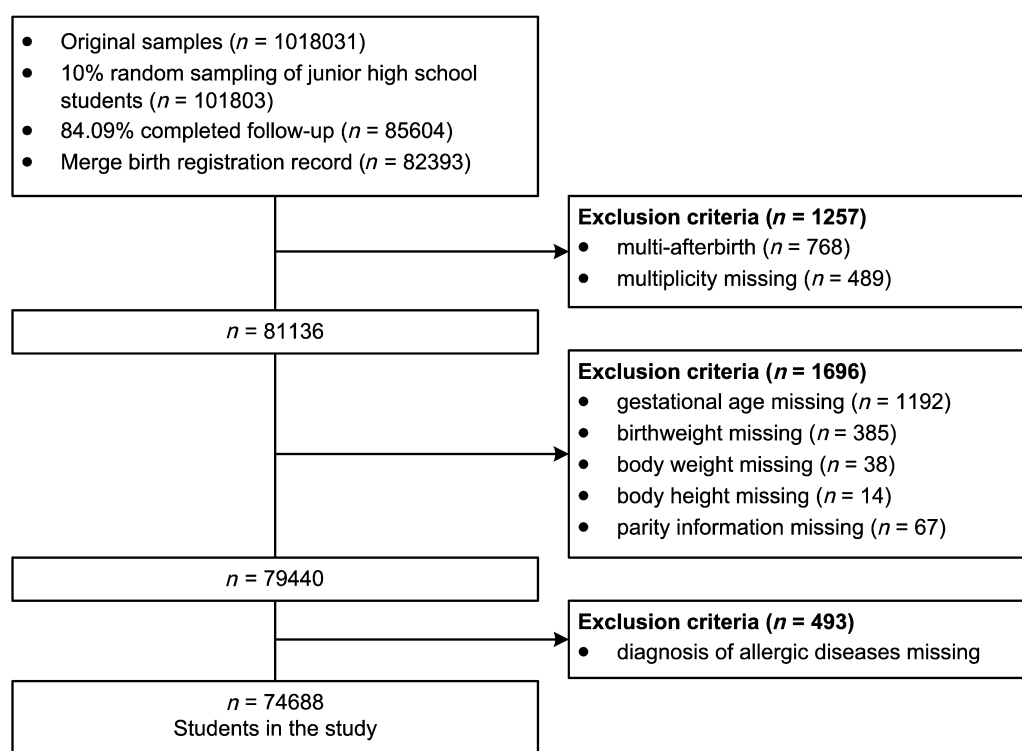


Figure 1. Flow chart of data collection and sampling frame.

questions 'Has your child ever been diagnosed as having AR by a physician?' and 'Has your child ever had a problem with sneezing, or a runny or blocked nose, when your child did not have a cold or the flu?'

Statistical analysis

Demographic characteristics (e.g. fetal growth) and odds ratios (ORs) with 95% confidence intervals [CI] were calculated using the logistic regression models to examine overall associations among fetal growth, BMI status, and allergic diseases. The analysis was adjusted for the child's age, paternal education and environmental tobacco smoke. To further assess the interaction between BMI status with birthweight and fetal growth, BMI status was divided into four categories, as <17, 17–21 (reference category), 21–23, and >23 kg/m². Based on the definition of Taiwan Ministry of Health and Welfare, individuals with a BMI of 21–23 and greater than 23 are considered overweight and obese, respectively. These category limits were selected based on the percentiles obtained from the standard age and gender BMI distribution. The interaction was tested by adding a product term in the regression model. All hypothesis testing was two

sided at the 0.05 significance level and was performed using SAS software version 9.3 (SAS Institute, Inc., Cary, NC, USA).

Results

The demographic characteristics of subjects stratified by gender are given in Table 1. Overall, except age and parental education, typical demographic distributions were different between genders. As expected, school-aged boys had higher BMI measurements. On the other hand, increasing gestational age and fetal growth was higher in girls. Boys were more likely to live in homes where residents or visitors smoke in the home on a regular basis. Of 74 688 mainly 13–15-year-old participants (37 878 boys and 36 810 girls), the estimated prevalence for AD was 7.6 per cent and for AR was 22.4 per cent, respectively (Table 2). In general, atopic disorders were slightly more common in boys than girls (data not shown). It is noteworthy that the risk of developing AD was also associated with school-aged BMI. For example, adolescents with high BMI measures (>23 kg/m²) were more likely to develop AD (OR 1.41, 95% CI 1.32, 1.51) than their peers with normal BMI measurements (17–21 kg/m²,

Table 1. Demographic characteristics of the study participants

	All <i>n</i> = 74 688	Boys <i>n</i> = 37 878	Girls <i>n</i> = 36 810	<i>P</i> value
At birth				
Gestational age, week (%)				0.001
<37	2.2	2.3	2.1	
37–40	91.1	91.4	90.9	
>40	6.7	6.3	7.0	
Fetal growth (%)				<0.0001
SGA	10.5	9.5	11.5	
AGA	79.6	82.4	76.8	
LGA	9.9	8.1	11.7	
At school age				
Body mass index, kg/m ² (%)				<0.0001
<17	11.0	11.4	10.5	
17–21	53.4	52.9	54.0	
21–23	16.3	15.1	17.4	
>23	19.4	20.6	18.1	
Age, years (%)				0.133
<13	8.9	8.9	8.9	
13–14	67.7	67.8	67.4	
≥15	23.5	23.2	23.7	
Family characteristics				
Parental education, years (%)				0.196
≤6	36.4	36.1	36.8	
7–9	21.4	21.5	21.4	
10–12	27.6	27.7	27.4	
≥13	14.6	14.8	14.4	
Number of smoker at home (%)				<0.0001
0	39.6	39.6	39.6	
1	44.5	43.8	45.3	
>1	15.9	16.6	15.2	

reference group). Comparable findings were likewise found for AR that there is an increased risk of developing AR associated with increasing school-aged BMI.

Despite lack of an apparent association of restricted fetal growth (SGA) alone with either AD or AR (Table 2), an elevated risk of AD was seen in those with SGA combined with higher adolescent BMI (Table 3). For example, adolescents with SGA and a high BMI (BMI >23 kg/m²) had a higher risk of developing AD compared with those with AGA and BMI of 17–21 kg/m² (reference group) with covariate adjustment (OR 1.64, 95% CI 1.37, 1.97). Of note, despite the increased risk of developing AD due to a combination of BMI and fetal growth status, the individual interactions between BMI and fetal growth status on atopic disorders did not reach statistical significance.

Compared with the observations for AD, there was interplay between SGA and adolescent BMI (current) with respect to the increasing the risk of developing AR (Table 3). Yet, once again, there was no interaction between the individual components (e.g. fetal growth and BMI) on AR.

Comment

The interactions of developmental status at birth and BMI on the risk of adolescent AD and AR have been largely unexplored. The current study uses a novel linkage to demonstrate the combined influence of fetal growth and excess body mass on the risk of atopic disorders in adolescence. Although there was no significant role of SGA alone (Table 2), those who combined SGA and catch-up over growth, as reflected by

Table 2. The association of fetal growth and BMI with atopic dermatitis and allergic rhinitis

	<i>n</i>	% ^a	OR (95% CI) ^b
<i>Atopic dermatitis</i>	74 688	7.6	
Fetal growth			
SGA	7834	7.7	1.02 (0.94, 1.12)
AGA	59 484	7.7	1.00 (Reference)
LGA	7370	7.2	0.96 (0.87, 1.05)
BMI, kg/m ² (school age)			
<17	8184	6.1	0.84 (0.76, 0.93)
17–21	39 917	7.0	1.00 (Reference)
21–23	12 135	8.3	1.19 (1.11, 1.29)
>23	14 452	9.7	1.41 (1.32, 1.51)
<i>Allergic rhinitis</i>	73 926	22.4	
Fetal growth			
SGA	7738	22.2	1.04 (0.98, 1.10)
AGA	58 888	22.5	1.00 (Reference)
LGA	7300	21.5	1.01 (0.95, 1.07)
BMI, kg/m ² (school age)			
<17	8098	21.4	0.95 (0.90, 1.01)
17–21	39 524	21.9	1.00 (Reference)
21–23	12 000	23.1	1.07 (1.02, 1.12)
>23	14 304	23.7	1.08 (1.03, 1.13)

^aThe percentage of cases in each category.^bOR estimated by multiple logistic regression model and adjusted by child gender, child age, parental education, and environmental tobacco smoke.

excess body mass in adolescence, tended to have a higher risk of developing AD and AR. Compared with those with AGA and school-aged BMI of 17–21 kg/m², the risk of developing AD increased 64 per cent among their adolescent peers with SGA and high BMI (BMI >23 kg/m²) (OR 1.64, 95% CI 1.37, 1.97). This

risk for the combination was higher than that for either SGA (OR 1.04, 95% CI 0.91, 1.17) or high school-aged BMI (BMI >23 kg/m²) (OR 1.41, 95% CI 1.31, 1.52) alone (Table 3). Low birthweight and high adolescent BMI were likewise associated with increased risk of AD and AR in our secondary analysis since both are highly correlated (Spearman correlation = 0.57, *P* < 0.05, data not shown).

Steffensen also observed an increased risk of AD among young adults with low birthweights (<2501 g).⁹ This finding may reflect the observation that underweight infants with more signs of intrauterine growth restraint were often fatter than their peers 5 years later.²⁰ Of note, SGA at birth is indicative of an impaired fetal growth course presumably due to poor nutrient supplies during gestation. The adaptation to intrauterine deficiencies appears to programme baby for rapid postnatal growth. Mechanisms that regulate postnatal catch-up growth may well influence associations between small size at birth and risks for disease in adulthood. The Barker hypothesis contends that the malnourished fetus is programmed to exhibit a 'thrifty phenotype' with increased food intake and fat deposition. Faced with available surplus calories, such individuals are disposed to develop obesity and other metabolic syndromes at adulthood presumably due to alterations in homeostatic regulatory mechanisms.²¹ The metabolic consequences in children born SGA might be mitigated by ensuring an appropriate catch-up path to reach the normal growth curve by limiting calories and preventing excess weight gain.

A recently proposed mechanism suggests that the interaction between SGA, obesity, and atopic

Table 3. The association of fetal growth with atopic dermatitis and allergic rhinitis after stratify by BMI at school age

		Body-mass index (kg/m ²)							
		<17		17–21		21–23		>23	
		<i>n</i>	OR (95% CI)	<i>n</i>	OR (95% CI)	<i>n</i>	OR (95% CI)	<i>n</i>	OR (95% CI)
<i>Atopic dermatitis</i>									
SGA	1118		0.82 (0.63, 1.05)	4314		1143		1259	
AGA	6559		0.86 (0.77, 0.96)	31 933		9601		11 391	
LGA	507		0.57 (0.37, 0.88)	3670		1391		1802	
<i>P</i> for interaction	0.580								
<i>Allergic rhinitis</i>									
SGA	1107		1.05 (0.91, 1.22)	4265		1125		1241	
AGA	6489		0.96 (0.90, 1.03)	31 618		9500		11 281	
LGA	502		0.79 (0.63, 1.00)	3641		1375		1782	
<i>P</i> for interaction	0.275								

disorders may involve intrauterine programming of the developing endocrine and immune systems through epigenetic modulation of critical genes.^{22–24} SGA affects multiple organ systems by interrupting developmental processes such as programmed apoptosis or by producing lasting changes in key regulatory factors. Both of these are associated with a persistent change in gene expression. Epigenetic modulation of transcription is a potential contributor in this regard. Epigenetic adaptation may be the key for the successful fetal response to *in utero* malnutrition. Although this strategy may be required for immediate fetal and perinatal development, its lasting character may also compromise later aspects of metabolic health. Thus, additional studies to define these mechanisms are imperative.

Since obesity is an independent risk factor for systemic inflammation,^{25–28} it may produce a pro-inflammatory environment conducive to the development of atopic illnesses. Collectively the current analyses further support the hypothesis that fetal growth restriction may play an important role in the subsequent development of obesity and thus, the expression of an allergic vulnerability that formed early in life.

Reasons for the apparently greater susceptibility of adolescents with SGA and high BMI to AD vs. AR are unclear. Do the differences reflect differences in the probability of exposure to environmental agents or intrinsic reactivity of the underlying tissue defences? Routes of exposure are different for AD and AR but one would think that the skin with its epidermal cover would be better protected from exposure than the delicate airways. Although highly speculative at this point, perhaps then, the relative dermal vulnerability and/or susceptibility are again part of the programmed perinatal adaptation to prenatal stress. Why this would be helpful to the neonate is unclear but AD has actually been described as a combination of both, a compromised barrier and dysregulated immune response.^{29,30}

Several limitations to the current study need to be acknowledged. First, the current study used questionnaires to assess AD and AR, and may be less accurate than standard diagnoses provided by medical specialists. The ISAAC questionnaire however, is widely used and has been cross-validated vs. physician-based diagnoses.^{31,32} Second, the potentially more specific developmental measures such as birth length and head girth were not available because of the retrospec-

tive study design. Third, because of the cross-sectional nature (e.g. the comparison of adolescent obesity and allergic disorders) of the current analysis, the possibility of reverse causality or residual confounding cannot be ruled out despite the multivariable adjustments for key allergenic risk factors (e.g. environmental tobacco smoke). Whether obesity promotes the emergence of allergic diseases in SGA children, helps to maintain it, or actually exaggerates it clearly warrants additional investigation. Constraints on physical activity imposed by allergic diseases may promote inactivity and weight gain and thus should also be considered. Fourth, the influence of symmetric vs. asymmetric SGA was not evaluated. Asymmetric SGA mainly results from maternal malnutrition, placental dysfunction, and maternal smoking in the last trimester.^{4,33} Since a significant number of those born SGA are asymmetric and predisposed to subsequent metabolic disorders, evaluating this interaction with atopic illnesses would be a logical step in a future analysis.^{4,33} Finally, though selection bias can be a problem in retrospective studies, this was minimised in the current analyses by using a computerised random sampling methodology. The strengths of the current study included a well-powered sample size and population-based study design. The study provided an unusual opportunity to examine the relationship between perinatal events and their potential immunological consequences in adolescence. The nationwide character of the data set should reduce common selection biases even further and enhance the overall confidence in the results. Because of the large sample size, numerous potential confounders were amenable to control within the statistical analysis. In addition, focus on singleton child increases the validity and generality of the results by decreasing misclassification and complicating influence of multiparous births.

Conclusion

This study provides the first evidence that those who were born SGA and showed potentially sufficient catch-up growth to be later classified as obese may increase the risk of developing AD and AR. These observations suggest that avoiding excessive weight gain is important among SGA infants to prevent the development of allergic diseases. This study suggests that examining postnatal feeding practices and regulating the availability of surplus calories for SGA

infants may be important. Furthermore, generalised weight control among children and adolescents might be an important strategy to reduce the risk of subsequent allergic diseases.

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