

Original Article

Birth size effect on pulmonary functions and atopic sensitization in preadolescence

İlknur Bostanci,¹ Dilek Dilli² and Yıldız Dallar²

Departments of ¹Paediatrics Allergy and Asthma and ²Paediatrics, Ankara Training and Research Hospital, Ankara, Turkey

Abstract *Background:* The purpose of the present paper was to examine whether low birth size is associated with reduced pulmonary function and increased atopic sensitization in preadolescence.

Methods: A cohort of 25 small-for-gestational-age (SGA) infants and an age- and sex-matched comparison group of 29 appropriate-for-gestational-age (AGA) infants born in 1993/94 were studied in preadolescence. Forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1), and forced expiratory flow when 25–75% of FVC is expired (FEF_{25–75%}) were measured using a spirometer. Atopic sensitization was assessed on serum total IgE levels and skin prick tests (SPT) to common allergens.

Results: There were positive correlations among FEV1 ($r = 0.30$, $P = 0.001$), FVC ($r = 0.20$, $P = 0.03$), and FEF_{25–75%} ($r = 0.5$, $P = 0.001$) and ponderal index (PI), although the FEV1/FVC ratio was not correlated with birth size. Mean value of serum total IgE was higher in SGA (106.0 ± 73.4 IU/mL) than AGA children (71.4 ± 67.1 IU/mL; $P = 0.02$). PI under 10th centile was associated with high IgE levels ($P = 0.04$, odds ratio, 3.2; 95%CI: 1.0–9.8). The overall prevalence of atopy was 14.8% and there was no significant difference between the groups ($P > 0.05$).

Conclusion: Preadolescents who were born SGA with low birth size compared to controls had reduced pulmonary function. In preadolescence the prevalence of atopy is not higher in SGA than AGA children, although low PI at birth is associated with high IgE levels. Further follow up of this cohort is required to establish the pattern of pulmonary functions and atopic sensitizations in relation to birth size.

Key words atopy, birth size, preadolescence, pulmonary function.

It has been suggested that fetal growth plays an important role in lung maturation. There is currently interest in the role of fetal growth patterns in the inception of asthma.¹ A few studies have found a relationship between lower birthweight and asthma in children,^{2,3} but most have not.^{4–6} There are few data on the relationship between lower birthweight and asthma beyond late adolescence because of paucity of reliable data for individuals followed prospectively from birth to adulthood. In one study lower bodyweight at birth was shown to be associated with reduced forced expiratory volume and vital lung capacity with an increased risk for asthma.⁷

Because anthropometric parameters at birth reflect fetal growth and to some extent intrauterine and nutritional status, several studies have examined the relationship between these measures and atopic disease. Birthweight and length have been associated with later asthma.⁸ It has been speculated that, when the demand for nutrients later in gestation are no longer fully met in these rapidly growing fetuses, the differentiation of specific thymus-derived helper lymphocytes from T-helper 2 (Th2) type towards Th1 type lymphocytes may be permanently impaired,

which will in turn lead to exaggerated IgE responses and atopic phenomena later in life.⁹ Arshad *et al.* suggested that low birthweight was associated with atopic sensitization assessed by skin prick test (SPT) in 2-year-old infants.¹⁰ Data from a Finnish birth cohort indicated a U-shaped association of ponderal index (PI) at birth and atopy in terms of positive SPT at age 31 years.¹¹ In addition, an increased risk of atopic dermatitis was found among children with increased gestational age and birthweight.¹² Therefore, the aim of the present study was to examine whether low birth size is associated with reduced pulmonary function and increased atopic sensitization in preadolescence.

Methods

Study population and study design

This was a cohort study in which all subjects were selected according to their birth size, obtained from maternal copies of birth records at Ankara Training and Research Hospital. Healthy, singleton infants (>38 weeks) were eligible for inclusion if born to a Turkish mother who did not smoke in pregnancy. Infants with congenital abnormalities or with neuromuscular or cardio-respiratory disorders were ineligible, as were those who required any ventilatory assistance during the neonatal period. Gestational age, gender, birthweight and length were obtained from the birth data. Infants were classified according to birthweight and gestational age using the sex-specific Child Growth–Development

Correspondence: Dilek Dilli, MD, Varlık Mah. Yüzücü Sk. Anadolu Apartment 27/6, Yenimahalle, Ankara 06070, Turkey. Email: dilekdilli2@yahoo.com

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curves for Turkey,¹³ and Battaglia and Lubchenco classification.¹⁴ Infants with birthweight <10th centile were classified as small for gestational age (SGA) with cut-off of 2500 g at term, whereas those in the 10th–90th centile were classified as appropriate for gestational age (AGA). To define intrauterine growth retardation (IUGR) PI (weight/height³ × 100) was estimated from the birth data and <10th centile was defined as IUGR.^{14,15}

In 1993, according to birth data, 55 babies were born at term with a birthweight <2500 g and defined as SGA. In preadolescence, approximately 8–9 years later, we recalled SGA children by mail. Twenty-five children (45.4%) participated to the study due to family moves. The control group was randomly selected from the same birth data and included AGA children with birthweight >2500 g at term. They were also invited in preadolescence, and 29 age- and sex-matched AGA children participated in the study. A meeting at which all parents and children were more extensively informed and could ask questions was arranged. After full explanation of the study, informed written consent was obtained from the parents of the children. The study was approved by the local ethics committee of Ankara Training and Research Hospital.

Questionnaires

The self-administered parental questionnaire included the International Study of Asthma and Allergies in Childhood core questions on symptoms of asthma, which have been described elsewhere.¹⁶ Children were defined as having 'diagnosed asthma' if parents reported that a doctor had diagnosed asthma in the child at least once. Children were defined as having 'current wheeze' when a parent reported at least one episode of wheezing in the past 12 months.

Family history of allergic disease was defined by the presence of atopic dermatitis, allergic rhinitis, hayfever, or asthma in either parent or any sibling. Information concerning breast-feeding >6 months, passive smoking, and family income per month (defined as low if <US\$350) was also gathered.

Physical measures

At the beginning of the study, bodyweight was determined to the nearest 0.5 kg with the child lightly clothed using Seca patient scales (Seca Scales; Vogel & Halke, Hamburg, Germany). Body height was measured, using the Leicester Height Measure (Child Growth Foundation, Leicester, UK) to the nearest 0.5 cm.

Pulmonary function tests

The standard pulmonary function test used to measure airway obstruction is the forced expiratory spirometer. This allows an assessment of the rate of change in volume that occurs as a function of time. The pulmonary function tests were performed using a spirometer, MIR Spirobank (Rome, Italy) with an attached printout. The output provided numerical as well as graphical data, enabling the detection of any error in subject technique. The spirometer was calibrated daily for use.

All assessments were carried out by the same examiner at the Department of Allergy and Asthma. The examiner demonstrated to each subject the technique for measuring Forced vital capacity (FVC). The subjects were given an opportunity to practice. Later each subject was required to perform a minimum of three repro-

ducible FVC measures (within 5% of maximal FVC). The spirometer that produced the highest sum of FVC and forced expiratory volume in 1 s (FEV1) was used in the analysis.¹⁷ FEV1, the ratio of FEV1/FVC, and forced expiratory flow when 25–75% of FVC was expired (FEF_{25–75%}) were used as markers of airway obstruction. The values are expressed as percentage predicted for weight, height, age, and gender using standard reference values.¹⁸

Blood sampling and laboratory analysis

The children provided blood samples following parental approval. Blood was collected for all subjects ($n = 54$) to measure the serum level of total IgE on nefelometry (Beckman-Coulter, Krefeld, Germany) with a cut-off of 100 IU/mL. All samples were analyzed in one laboratory (Microbiology-Serology Laboratory of Ankara Training and Research Hospital).

Skin prick tests

Atopic sensitization was assessed on epidermal skin tests to common allergens including alternaria (mold), grasses, dactyls glom, salix, latex, cockroach (*Blatella germanica*), cat fur, milk, cacao, *Dermatophagoides pteronyssinus*, egg whole, strawberry, tomatoes, banana, groundnut (15 aeroallergen stallergen) by a professional technician using standardized allergen extracts and control solutions provided by ALK (Horsholm, Denmark). Allergens were applied on the volar side of the left forearm according to the manufacturer's recommendations. Positive (histamine 10 mg/mL) and a negative (diluent) controls were applied as well, and a weal diameter >3 mm after subtraction of the negative control was defined as a positive skin reaction. Atopy was defined as the presence of at least one positive skin reaction to any allergen tested.

Statistical analysis

Statistical analysis was performed using SPSS 10.0 for Windows (SPSS, Chicago, IL, USA). Results are expressed as means ± SD. Separated groups were not normally distributed according to Kolmogorov–Smirnov test. Mann–Whitney *U*-test was used to evaluate group differences in continuous variables. χ^2 test was used to compare the categorical variables. Spearman rank correlation test was used to assess correlation between birth size and pulmonary function parameters. Associations of atopy and risk factors for atopic sensitization with high total IgE levels were analyzed on binary logistic regression. $P \leq 0.05$ was considered to be significant. The size of the effect of each of the risk factors was measured using odds ratio (OR) and 95% confidence interval (95%CI).

Results

A total of 54 children were studied whose birthweight and length were collected from birth data. All subjects were born at term and divided into two groups according to birthweight; 25 subjects (46.3%) were born <2500 g and 29 subjects (53.7%) were born >2500 g. Birthweight, birth length and PI were significantly lower in the SGA than the AGA group (respectively, $P = 0.001$, $P = 0.002$ and $P = 0.001$). In 88% of SGA infants PI was <10th centile and defined as IUGR. Gender distribution was 52% female in SGA and 48.2% female in AGA ($P > 0.05$).

At the time of the study mean age was 8.6 ± 0.6 years and 8.5 ± 0.6 years, respectively, in SGA and AGA children ($P > 0.05$). There was also no significant difference between the groups according to weight and height distributions ($P > 0.05$ and $P > 0.05$). Pulmonary functions were analyzed in two groups and expressed as percentage predicted for weight, height, age, and gender using standard reference values. FEV1, FVC, and FEF_{25–75%} were significantly low in the SGA group, although there was no statistically significant difference between the two groups according to FEV1/FVC ratio (Table 1).

Mean value of total IgE was higher in SGA children (106.0 ± 73.4 IU/mL) than in AGA children (71.4 ± 67.1 IU/mL; $P = 0.02$; Table 1).

The prevalence of atopy (at least one positive SPT reaction) was 24.0% in SGA children and there was no significant difference between the two groups ($P > 0.05$; Table 1). The most common sensitizations were to grass pollens, *Dermatophagoides pteronyssinus*, and cockroach (*Blatella germanica*), respectively.

Correlation between birth size and pulmonary function parameters were assessed in preadolescence. We found that there were positive correlations among FEV1 ($r = 0.40$, $P = 0.001$), FVC ($r = 0.21$, $P = 0.02$), and FEF_{25–75%} ($r = 0.03$, $P = 0.001$) and birthweight. PI was also positively correlated with FEV1 ($r = 0.30$, $P = 0.005$), FVC ($r = 0.20$, $P = 0.03$) and FEF_{25–75%} ($r = 0.50$, $P = 0.001$). FEV1/FVC ratio, however, was not correlated with birth size. Scatter-plots of FEV1 against birthweight is shown in Figure 1, and that of FVC against birthweight is shown in Figure 2. A representative flow–volume and volume–time curve of an 8-year-old girl from the SGA group showing declining FEV1 and moderate airway obstruction is seen in Figure 3.

According to parental questionnaire, current wheeze or doctor-diagnosed asthma prevalence in the previous 12 months was 14.8% in all children. The overall prevalence of breast-feeding >6 months (compared with 0–6 months) was 64.8% and exposure to passive smoking was present in 22.2% of all children.

Family income per month was reported to be under US\$350 in 59.3% of all families.

At the time of the study all children were also assessed for atopic sensitization by serum total IgE levels and SPT to common allergens. Associations of atopy and risk factors for atopic sensitization with high total IgE levels were analyzed using logistic regression. As shown in Table 2, birthweight, gender, current wheeze or doctor-diagnosed asthma in previous 12 months, atopy, family history of allergic disease, breast-feeding >6 months (compared with 0–6 months), passive smoking, and family income did not have a significant association with high IgE levels, but PI under 10th centile was associated with high IgE levels ($P = 0.04$, OR, 3.2; 95%CI: 1.0–9.8). An inverse correlation between PI and total IgE levels is seen in Figure 4 ($r = -0.36$, $P = 0.01$).

Discussion

Infants with reduced birth size have greater morbidity and mortality than to AGA age-matched infants in later life. SGA is defined as birthweight lower than the population norms. IUGR is defined as failure of normal fetal growth caused by multiple adverse effects on fetus due to process that inhibits normal growth potential of fetus. These terms are related but not synonymous. Not all IUGR infants are small enough to fit the qualifications for SGA. PI is used to determine those infants whose soft-tissue mass is below normal for their stage of skeletal development.¹⁵ In the present study population, according to birthweight and PI, 88% of the SGA infants had IUGR.

Intrauterine growth retardation is associated with an increased risk of developing adult diseases, such as asthma, hypertension, type 2 diabetes mellitus and coronary heart disease. This has led to the suggestion that these diseases are programmed by an inadequate supply of nutrients or oxygen *in utero* or immediately after birth. In a study based on nine SGA infants whose gestational age ranged from 33–41 weeks, Dahms *et al.* reported elevated compliance and crying vital capacity but normal functional residual capacity when compared with AGA infants and concluded that

Table 1 Group characteristics according to birthweight

		SGA (birthweight <2500 g) (n = 25)	AGA (birthweight >2500 g) (n = 29)	P
At birth	Gender (girl/boy)	13/12	14/15	n.s.
	Birthweight (g)	2284 ± 133	3499 ± 400	<0.05
	Birth length (cm)	47.8 ± 1.5	50.5 ± 1.2	<0.05
	Ponderal index (weight/height ³)	2.09 ± 0.2	2.67 ± 0.2	<0.05
At the time of the study	Age (years)	8.6 ± 0.6	8.5 ± 0.6	n.s.
	Weight (kg)	27.1 ± 2.8	25.5 ± 3.3	n.s.
	Height (cm)	128.0 ± 8.1	128.1 ± 6.7	n.s.
Pulmonary function parameters	FEV1(%)	84.8 ± 8.5	95.0 ± 8.7	<0.05
	FVC(%)	86.7 ± 7.5	92.9 ± 11.6	<0.05
	FEV1/FVC(%)	89.8 ± 5.9	92.6 ± 5.0	n.s.
	FEF _{25–75%}	88.4 ± 8.0	102.3 ± 19.3	<0.05
Atopic sensitization	Total IgE (IU/ml)	106.0 ± 73.4	71.4 ± 67.1	<0.05
	Prevalence of atopy (%)	6 (24)	2 (6.9)	n.s.

AGA, appropriate for gestational age; FEF_{25–75%}, forced expired flow at 25–75% of FVC; FEV1, forced expired volume in 1 s; FVC, forced vital capacity; SGA, small for gestational age.

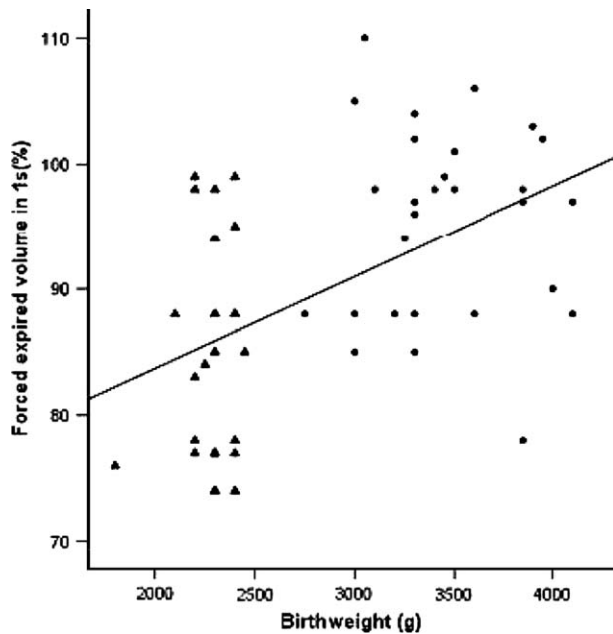


Fig. 1 Forced expired volume in one second (%) in preadolescence plotted against birthweight (g) according to birthweight status ($P = 0.001$; $r = 0.40$). (▲) Small for gestational age; (●), appropriate for gestational age.

intrauterine stress leads to increased pulmonary maturity.¹⁹ In two cohort studies, low-birthweight infants were evaluated for subsequent childhood lung function in preadolescence and it was confirmed that they had reduced expiratory flows and a higher prevalence of diagnosed asthma.^{20,21} We have shown that a lower birthweight and PI at birth are associated with lower pulmonary

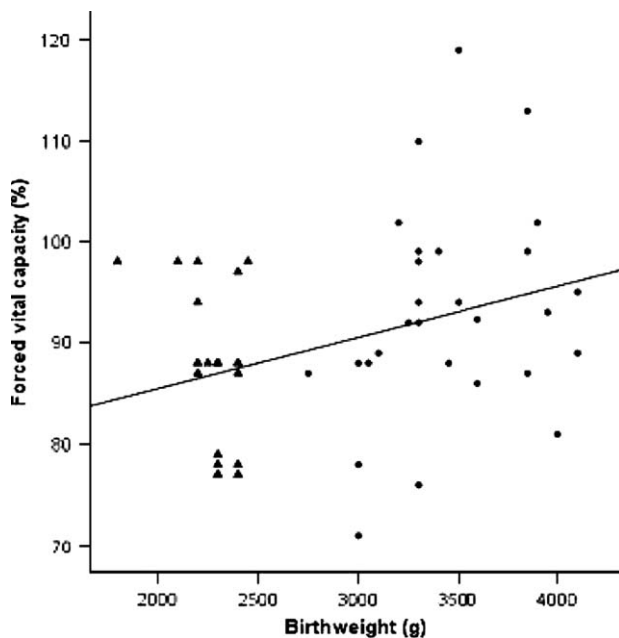


Fig. 2 Forced vital capacity (%) in preadolescence plotted against birthweight (g) according to birthweight status ($P = 0.02$; $r = 0.21$). (▲) Small for gestational age; (●), appropriate for gestational age.

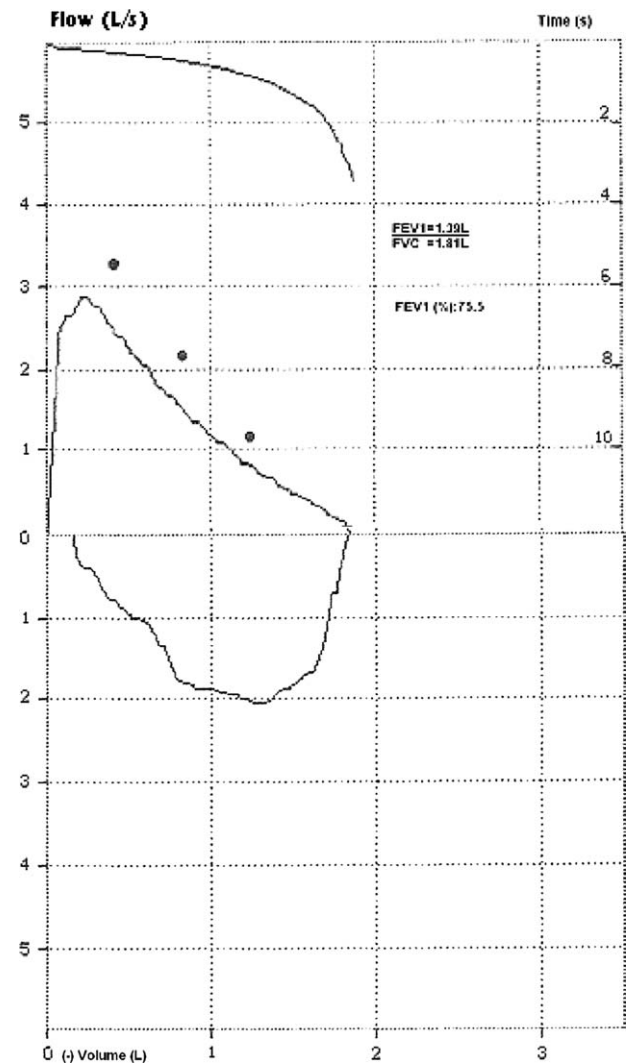


Fig. 3 Flow-volume and volume-time curve of an 8-year-old girl from the small-for-gestational-age group. Both curves reflect moderate airway obstruction. FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity.

function among preadolescents in a birth cohort studied at 8–9 years of age. Although the mechanisms linking early lung development with lung function in later life are unknown, impaired airway and alveolar growth may be important. The relationship between lung function and birthweight in childhood supports the fetal programming hypothesis.²² SGA infants tended to have lower FEV1, FVC and $FEF_{25-75\%}$, but not lower FEV1/FVC ratios, which indicates a restrictive rather than an obstructive deficit. Thinness at birth is also thought to result from fetal undernutrition in late gestation. The restrictive deficit observed in thin babies is in keeping with an impairment of lung growth in late gestation, because alveoli appear only in the last trimester of gestation.²³ Birthweight is a crude marker of fetal growth, and measures of body proportion at birth may be more sensitive indicators of impaired prenatal growth during critical periods of immunological and pulmonary development. For example, a large head circumference at birth was associated with elevated total IgE, as

Table 2 Atopy and risk factors for atopic sensitization and high total IgE

Variable	Category	<i>n</i>	Total IgE (IU/mL)	OR (95%CI)	<i>P</i> [‡]
Birthweight (g)	>2500	29	71.4 ± 67.1	0.9 (0.2–3.1)	n.s
	<2500 [‡]	25	106.0 ± 73.4		
Ponderal index (weight/height ³)	>10th centile	29	65.5 ± 42.5	3.2 (1.0–9.8)	<0.05
	<10th centile [‡]	25	112.9 ± 59.2		
Gender	Boy	27	88.3 ± 59.2	0.5 (0.2–1.2)	n.s
	Girl [‡]	27	86.5 ± 53.2		
Wheezing/asthma	No	48	80.8 ± 50.7	5.9 (0.9–35.0)	n.s
	Yes [‡]	6	140.5 ± 70.5		
Atopy	No	46	85.7 ± 59.0	0.45 (0.1–1.8)	n.s
	Yes [‡]	8	97.1 ± 32.3		
Family history of allergic disease	No	46	110.6 ± 36.4	2.1 (0.5–8.5)	n.s
	Yes [‡]	8	83.4 ± 57.8		
Breast-feeding (>6 months)	No	19	87.1 ± 42.8	1.5 (0.6–3.6)	n.s
	Yes [‡]	35	87.6 ± 62.3		
Passive smoking	No	42	82.7 ± 56.0	1.4 (0.6–3.6)	n.s
	Yes [‡]	12	104.0 ± 54.1		
Low income (<US\$350 per month)	No	22	75.1 ± 61.3	0.6 (0.2–1.7)	n.s
	Yes [‡]	32	95.8 ± 50.9		

[‡]Logistic regression; [‡]reference categories.
CI, confidence interval; OR, odds ratio.

well as with the development of asthma in later life.²⁴ A large head size at birth has been interpreted as a sign of rapid fetal growth from early in gestation that makes the fetus vulnerable to undernutrition in late gestation.²⁵ We had no information on birth head circumference in the present study.

Lau *et al.* studied 800 children to analyze determinants of lung function in 7-year-old children with different wheezing patterns (early, persistent and late onset) and they found that determinants of impaired lung function in the group of current wheezers were: time in years since first wheeze, a parental his-

tory of atopy, current sensitization to indoor allergens, elevated cord blood IgE levels and low PI at birth.²⁶ In the present study, there was a significant difference according to total IgE levels between SGA and AGA groups and low PI was an associated risk factor for high IgE levels in preadolescence.

In recent studies, SGA children were examined to determine association between measures of fetal growth and allergic disease at age 5–8 years. The data suggested that fetal growth and maturity were associated with atopic sensitization and total serum IgE levels in childhood.^{27,28} In another study, Kuyucu *et al.* investigated a clustered random sample of 8–11-year-old Turkish school children to delineate the prevalence and spectrum of, and to determine the causal and/or protective factors for atopic sensitization. They showed that children of atopic mothers had a different profile of risk factors associated with atopic sensitization, when compared with other children, and prenatal and early childhood events had important associations with atopic sensitization.²⁹ In the present study serum total IgE levels were higher in preadolescent SGA children than AGA children, although there was no significant difference between the two groups in terms of atopy. These findings suggest that both environmental and genetic factors determine the level of serum IgE in SGA children.³⁰ This may also be attributable to the small size of the study sample.

This is the first cohort study from Turkey to explicitly test the hypothesis that low birth size has an effect on reduced pulmonary function and that low PI is associated with high IgE levels in preadolescence.

This study has some methodological strengths: birthweight, birth length and PI data stem from medical records. Predispositional and environmental factors were taken into account on a logistic regression model. Because the optimal method of identifying SGA and IUGR infants remains unclear, we defined SGA as birthweight below the 10th centile for gestational age, and we

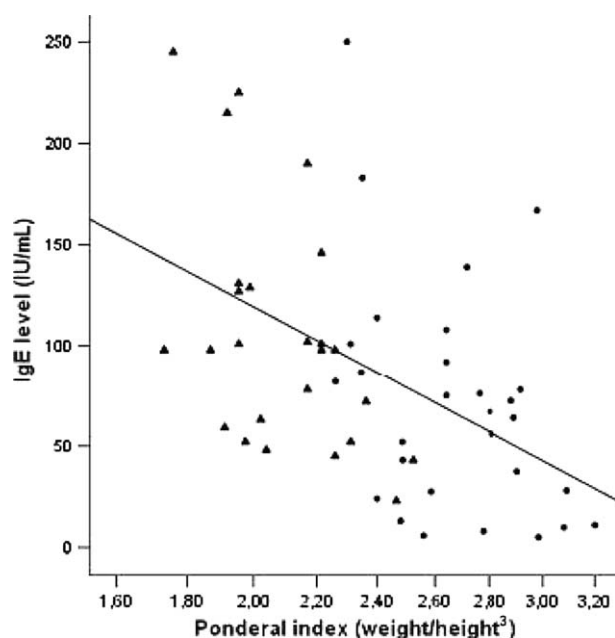


Fig. 4 Total IgE level (IU/mL) plotted against ponderal index at birth (weight/height³) according to birthweight status ($P = 0.01$; $r = -0.36$). (▲) Small for gestational age; (●), appropriate for gestational age.

used the PI to define IUGR according to the Battaglia and Lubchenco classification. The sample size evaluated at the time of the study was small (SGA, $n = 25$; AGA, $n = 29$) require cautious interpretation. Likewise, no account was available of maternal parity, perinatal treatment or lower respiratory tract infections during the first year.

In conclusion, the present results indicate that preadolescents who were born as SGA with low birth size had reduced pulmonary function compared to matched controls. In preadolescence, the prevalence of atopy is not higher in SGA than AGA children, although low PI at birth is inversely associated with high IgE levels. Further follow up of this cohort is required to establish the pattern of pulmonary functions and atopic sensitizations in relation to birth size.

References

- 1 Shaheen S. Discovering the causes of atopy. *Br. Med. J.* 1997; **314**: 987–8.
- 2 Schwarz J, Gold D, Dockery DW, Weiss ST, Speizer FE. Predictors of asthma and persistent wheeze in a national sample of children in United States. Association with social class, perinatal events, and race. *Am. Rev. Respir. Dis.* 1990; **142**: 555–62.
- 3 Weitzman M, Gortmaker S, Sobol A. Racial, social, and environmental risk factors for childhood asthma. *Am. J. Dis. Child.* 1990; **144**: 1189–94.
- 4 Sears MR, Holdaway MD, Flannery EM, Herbison GP, Silva PA. Parental and neonatal risk factors for atopy, airway hyperresponsiveness, and asthma. *Arch. Dis. Child.* 1996; **75**: 392–8.
- 5 Fergusson DM, Crane J, Beasley R, Horwood LJ. Perinatal factors and atopic disease in childhood. *Clin. Exp. Allergy* 1997; **27**: 1394–401.
- 6 Demissie K, Ernst P, Joseph L, Becklake MR. Birth weight and preterm birth in relation to indicators of childhood asthma. *Can. Respir. J.* 1997; **4**: 91–7.
- 7 Stein CE, Kumaran K, Fall CHD, Shaheen SO, Osmond C, Barker DJP. Relation of fetal growth to adult lung function in South India. *Thorax* 1997; **52**: 895–9.
- 8 Leadbitter P, Pearce N, Cheng S *et al.* Relationship between fetal growth and the development of asthma and atopy in childhood. *Thorax* 1999; **54**: 905–10.
- 9 Godfrey KM, Barker DJP, Osmond C. Disproportionate fetal growth and raised IGE concentration in adult life. *Clin. Exp. Allergy* 1994; **24**: 641–8.
- 10 Arshad SH, Stevens M, Hide DW. The effect of genetic and environmental factors on the prevalence of allergic disorders at the age of two years. *Clin. Exp. Allergy* 1993; **23**: 504–11.
- 11 Xu B, Pekkanen J, Laitinen J, Jarvelin MR. Body build from birth to adulthood and risk of asthma. *Eur. J. Public Health* 2002; **12**: 166–70.
- 12 Olesen AB, Ellingsen AR, Olesen H, Juul S, Thestrup-Pedersen K. Atopic dermatitis and birth factors: Historical follow-up by record linkage. *Br. Med. J.* 1997; **314**: 1003–8.
- 13 Neyzi O, Binyildiz P, Alp H. Growth and development curves in Turkish children. *Med. Bull. Istanbul Med. Fac.* 1978; **41**: 3–22.
- 14 Battaglia FC, Lubchenco LO. A practical classification of newborn infants by weight and gestational age. *J. Pediatr.* 1967; **71**: 159–63.
- 15 Gomella TL, Cunningham MD, Eyal FG, Zenk KE. *Neonatology: Management, Procedures, On-Call Problems, Diseases, and Drugs*, 5th edn. Lange Medical Books/McGraw-Hill, New York, 2004.
- 16 Asher MI, Keil U, Anderson HR *et al.* International Study of Asthma and Allergies in Childhood (ISAAC): Rationale and methods. *Eur. Respir. J.* 1995; **8**: 843–91.
- 17 American Thoracic Society. ATS statement. Snowbird Workshop on standardization of spirometry. *Am. Rev. Respir. Dis.* 1979; **119**: 831–8.
- 18 European Community for Steel and Coal. Standardized lung function testing: Official statement of the European Respiratory Society. *Eur. Respir. J.* 1993; **6** (Suppl. 16): 1–100.
- 19 Dahms BB, Krauss AN, Auld PAM. Pulmonary function in dysmature infants. *J. Pediatr.* 1974; **84**: 434–7.
- 20 Kennedy JD, Edward LJ, Bates DJ. Effects of birth weight and oxygen supplementation on lung function in late childhood in children of very low birth weight. *Pediatr. Pulmonol.* 2001; **30**: 32–40.
- 21 Wjst M, Popescu M, Trepka MJ, Heinrich J, Wichmann HE. Pulmonary function in children with initial low birth weight. *Pediatr. Allergy Immunol.* 1998; **9**: 80–90.
- 22 Barker DJP. *Mothers, Babies and Disease in Later Life*. BMJ Publishing Group, London, 1994.
- 23 McCance RA, Widdowson EM. The determinants of growth and form. *Proc. R. Soc. Lond. B. Biol. Sci.* 1974; **185**: 1–17.
- 24 Gregory A, Doull I, Pearce N, Cheng S, Holgate S, Beasley R. The relationship between anthropometric measurements at birth: Asthma and atopy in childhood. *Clin. Exp. Allergy* 1999; **29**: 330–33.
- 25 Harding J, Liu L, Evans P, Oliver M, Gluckman P. Intrauterine feeding of the growth retarded fetus; can we help? *Early Hum. Dev.* 1992; **29**: 193–7.
- 26 Lau S, Illi S, Sommerfeld C *et al.* Transient early wheeze is not associated with impaired lung function in 7-yr-old children. *Eur. Respir. J.* 2003; **21**: 834–41.
- 27 Bolte G, Schmidt M, Maziak W *et al.* The relation of markers of fetal growth with asthma, allergies and serum immunoglobulin E levels in children at age 5–7 years. *Clin. Exp. Allergy* 2004; **34**: 381–8.
- 28 Palta M, Sadek-Badawi M, Sheehy M *et al.* Respiratory symptoms at age 8 years in a cohort of very low birth weight children. *Am. J. Epidemiol.* 2001; **154**: 521–9.
- 29 Kuyucu S, Saraclar Y, Tuncer A *et al.* Determinants of atopic sensitization in Turkish school children: Effects of pre- and post-natal events and maternal atopy. *Pediatr. Allergy Immunol.* 2004; **15**: 62–71.
- 30 Burney P, Malmberg E, Chinn S, Jarvis D, Luczynska C, Lai E. On behalf of the European Community Respiratory Health Survey. The distribution of total and specific serum IgE in the European Community Health Survey. *J. Allergy Clin. Immunol.* 1997; **99**: 314–22.