Birth weight and adult lung function: a within-pair analysis of twins followed up from birth

Kari Nikolajev, Heikki Koskela, Matti Korppi

Kuopio, Finland

Original article

Background: **The aim of the study was to evaluate whether there is any association between intrauterine growth and later lung function or bronchial reactivity in early adulthood in line with Barker's hypothesis.**

Methods: **Nineteen twin pairs with disproportionate intrauterine growth pattern were followed up from birth: either one of the pairs had intrauterine growth retardation (birth weight <2 SD) or the within-pair birth weight difference was >1.3 SD. Flow-volume spirometry, followed by isocapnic hyperventilation of cold air, was performed at the ages of 8-16 and 14-22 years in 1993 and 1999. Wilcoxon's matched-pairs analysis was used to compare smaller and larger twin pairs.**

Results: **In 1993, there were no significant differences between the groups in either spirometry or cold air challenge. In 1999, such a difference was found in forced expiratory volume % (FEV%) and forced expiratory flow (FEF) at 25%-75%, the smaller twin pairs having lower values. In 1993, nine subjects reacted to cold air (>9% decrease in FEV in 1 second). In 1999, only four subjects reacted to cold air, and they all belonged to the group of smaller twins (*P*=0.04).**

Conclusion: **Lung function evaluated by FEV% and FEF25-75 was lower and responses to cold air were more common at the median age of 16 years in twins with impaired intrauterine growth.**

World J Pediatr 2008;4(3):222-226

Key words: **birth weight; bronchial reactivity; intrauterine growth retardation; lung function**

Introduction

Foetal origin of diseases has been recognized in relationship with birth weight that reflects intrauterine growth, and chronic, mainly cardiovascular diseases in adults, called as Barker's hypothesis.[1,2] For lung diseases, there is increasing evidence that intrauterine environment can influence lung growth and development.[3] For example, the detrimental effect of maternal smoking on foetal lung growth seems to continue until adulthood.[3-5] The link from premature birth, respiratory distress syndrome and bronchopulmonary dysplasia to later pulmonary morbidity is well-known.[6-8] Since Barker's initial observations in the period of 1986-1991, many later studies have not been able to confirm the hypothesis.[9-11] In recent studies from the United Kingdom (UK), lung function was measured during the first year of life, and subnormal results were seen in children with intrauterine growth retardation (IUGR). The other risk factors for subnormal lung function were bronchopulmonary dysplasia, maternal smoking during pregnancy and genetic predisposition to asthma.[12-15]

Conventionally, twin studies have been used to distinguish genetic from environmental causes of diseases. Twin studies can also be used to test the hypothesis of foetal origins. By using within-pair analyses, the influence of environmental factors can be minimized, and by comparing monozygotic and dizygotic twins, even foetal and maternal factors can be separated.[16]

A group of children with disproportional intrauterine growth pattern from multiple pregnancies were followed up for 14 to 22 years from birth.[17-19] The present study was undertaken to evaluate the association of the intrauterine growth pattern with lung function and bronchial reactivity at teen age and in early adulthood using a within-pair analysis.

Methods

Subjects

As described,[17-19] a group of 67 children, born at

Author Affiliations: Department of Pediatrics (Nikolajev K) and Department of Pulmonary Medicine (Koskela H), Kuopio University and University Hospital, Finland; Paediatric Research Centre, Tampere University and University Hospital, Finland (Korppi M)

Corresponding Author: Matti Korppi, Pediatric Research Centre, Tampere University and University Hospital, Finland (Tel: +358-3-3551-8407; Fax: +358-3-3551-8420; Email: matti.korppi@uta.fi)

gestational age <38 weeks from multiple pregnancies, were followed up from birth in 1977-1985 to 1993. At the study visit in 1993, the children were 8 to 16 years old (median: 10 years), and none of them had asthma or other chronic lung diseases. In 1999, 53 (79%) of them were followed up at the age of 14 to 22 years (median: 16 years). Among them, 19 were twin pairs with disproportional intrauterine growth patterns: the pairs had either IUGR (birth weight <2 SD compared with Finnish foetal growth charts) or the within-pair birth weight difference was >1.3 SD.[17,20] These 19 twin pairs formed the subjects of the present study. The study was approved by the Ethics Committee of Kuopio University Hospital and Kuopio University. Informed consent was obtained from all study subjects.

Lung function

Basic lung function was measured by a pneumotachograph flow-volume spirometer (FVS) (Medikro 909, Medikro Ltd, Kuopio, Finland). The parameters included forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), forced expiratory flow at 50% of FVC (FEF50), and forced expiratory flow at 25%-75% (FEF25-75) of FVC. Lung function was measured according to the recommendations of the American Thoracic Society.[21] Three technically acceptable base-line FVS curves were obtained, and the curve with the best FEV1 was registered. Lung function data were standardized using height- and gender-related reference values, and were expressed as % of predicted.[21] FEV% (FEV1/FVC) was calculated from the absolute FEV1 and FVC values.

Cold air challenge

Cold air challenge was used to estimate bronchial reactivity. Isocapnic hyperventilation of cold air (IHCA) was carried out in a warm room as described in details earlier.[18,22,23] By using the base-line FEV1 value, the target minute ventilation was set to FEV1 × 25. Carbon dioxide was added to the inspired air, and the flow was calculated as the target minute ventilation ×0.05. Air containing water less than 1.75 mg/L was cooled in the heat exchanger, and released through a mouth piece. The temperature of the inspired air was continuously monitored and kept at -12ºC to -15ºC. The duration of hyperventilation was 4 minutes. Three

Table 1. Lung function parameters and cold air challenge results in the 19 twin pairs with disproportional intrauterine growth, measured at the median age of 10 years

Lung function and cold air challenge results	Smaller twin-pair [median (range)]	*P*	Larger twin-pair [median (range)]
Flow-volume spirometry			
FVC	98 (84-133)	NS	103 (78-120)
FEV1	97 (81-121)	NS	99 (65-171)
FEV%	89 (72-100)	NS	89 (73-97)
FEF50	93 (55-125)	NS	97 (57-125)
FEF25-75	90 (57-128)	NS	99 (51-130)
Cold air challenge			
FEV1 (%)	-6.3 (+12.8 to -24.3)	NS	-4.7 (+6.3 to -12.6)
Pathological result (>9% decrease in FEV1)	5 (26%)	NS	4 (21%)

Wilcoxon's rank-sum test was used in the statistical analysis of the data. FVC: forced vital capacity; FEV1: forced expiratory volume in 1 second; FEV%: FEV1/FVC; FEF50: forced expiratory flow at 50% of FVC; FEF25-75: forced expiratory flow at 25%-75% of FVC; NS: non-significant.

Table 2. Lung function parameters and cold air challenge results in the 19 twin pairs with disproportional intrauterine growth, measured at the median age of 16 years

Lung function and cold air challenge test results	Smaller twin-pair [median (range)]	*P*	Larger twin-pair [median (range)]
Flow-volume spirometry			
FVC	95 (77-149)	NS	108 (84-138)
FEV1	99 (76-112)	NS	103 (77-118)
FEV%	87 (69-96)	0.01	91 (68-100)
FEF50	84 (51-127)	NS	88 (53-134)
FEF25-75	93 (55-133)	0.03	102 (58-144)
Cold air challenge			
FEV1 (%)	-3.6 (+8.7 to -19.6)	NS	-4.8 (+1.3 to -8.8)
Pathological result (>9% decrease in FEV1)	4 (21%)	0.04	0

Wilcoxon's rank-sum test was used in the statistical analysis of the data. FVC: forced vital capacity; FEV1: forced expiratory volume in 1 second; FEV%: FEV1/FVC; FEF50: forced expiratory flow at 50% of FVC; FEF25-75: forced expiratory flow at 25%-75% of FVC; NS: non-significant.

technically acceptable FVS curves were obtained at 3, 5 and 10 minutes after hyperventilation, and the best FEV1 at each time were registered for the analysis. The maximal fall in FEV1, calculated from the highest pre-challenge and the lowest post-challenge FEV1, was used to express the response, and a fall of >9% was considered as pathological.[18,23]

Statistical analysis

The Wilcoxon's rank-sum test was used for comparisons of the results in the base-line FVS and in the IHCA challenge test within the 19 twin pairs with disproportional intrauterine growth, as well as in paired comparisons of the results in the same children 6 years apart.

Results

Lung function and cold air challenge results were measured in the children at the age of 8 to 16 years in 1996 (Table 1). No significant differences were shown by the within-pair analyses. The IHCA test revealed pathological responses in 9 (24%) children but no significant differences shown by the within-pair analyses.

Lung function and cold air challenge results were measured in the children at the age of 14 to 22 years in 1999 (Table 2). The originally smaller twin pairs had lower values in FVS; within-pair analyses showed that the FEV% and FEF25-75 between the groups were of statistical significance.

There were no significant differences in both groups between the measurements obtained at the two studies six years apart.

By the limits of 75% for FEV1 and FEV%, and 65% for FEF50 and FEF25-75, respectively, 5 (26%) children in the smaller twin-pair group and 2 (11%) in the larger twin-pair group had an abnormal FVS result with no significance.

In 1999, the IHCA test showed pathological responses in 4 (11%) children. They belonged to the group of smaller twin pair (P=0.04 vs the group of larger twin pairs). Two of them had pathological responses 6 years earlier. Thus, 78% (7/9) of the children with hyper-reactivity to cold air at the median age of 10 years had improvement in the following 6 years, including all 4 children in the group of larger twin pairs.

Discussion

In the present study, two factors related to the influence of intrauterine growth on lung function at teen age and early adulthood were observed. First, some evidence obtained by the sensitive measures of FEV% and FEF25-75, indicated the association of IUGR and decreased lung function. Second, an increased bronchial reactivity, being earlier present in >20% of the children of this cohort, continued only if intrauterine growth was deteriorated. These results are in agreement with Barker's hypothesis that prenatal programming of disorders is manifested in adults. However, the conditions leading to placental insufficiency like maternal obesity, smoking and diabetes rather than maternal malnutrition are the principal causes of IUGR in western countries.

Many authors have considered Barker's hypothesis and the conclusions based on the hypothesis too straightforward.[9-11] The main criticism has focused on the poor control of confounding factors, especially the length of gestation in cases of low birth weight. Actually, Barker's phenomenon means an adaptation of the foetus to the restricted environment leading to IUGR and further to chronic disorders. There is a risk of an impaired foetal growth in twin pregnancies, especially in monochorionic cases, starting after 30 to 32 weeks of gestation, and attributed to placental crowding, anomalous umbilical cord insertion and placental insufficiency.[24] There were only two studies,[25,26] in which birth weight was adjusted for gestational age as the present study. These studies were large population surveys. Rona et al[25] found that IUGR was linked with lowered lung function at the age of 5-11 years, and Wjst et al[26] found that IUGR was linked with increased bronchial reactivity at the age of 5-14 years. In addition, birth weight was linearly independent from other factors associated with adult FEV1 and FVC in two historic prospective follow-up studies,[27,28] although it was not associated with asthma or wheezing. It was also found in two recent birth cohort studies from the UK and Finland.[29,30]

At an early age in this cohort, lung flows were, especially in the area of small airways, marginally lower in former IUGR children than in those with birth weight as appropriate for gestational age.[17] In the present study, a within-pair analysis showed a corresponding result at 16-22 years of age, but not 6 years earlier, obviously because of insufficient power for the within-paired analysis. In theory, intrauterine growth retardation may interfere with the growth of the lungs, which later should be manifested as lowered lung volume.[26] In contrast, lung flows were affected more than FVC in the present study, as was observed in the study of lung function in infancy.[12-15]

At early age in this cohort, the degree of bronchial reactivity, measured by cold air challenge, methacholine challenge and exercise challenge by free running outdoors,[18,19] was not associated with the intrauterine growth pattern. In the present study, bronchial hyper-reactivity was present in less than 6 years earlier in the former IUGR children only. Thus, the reactivity normalized in over 75% of the children. In a study, the improvement of lung function in the former low birth weight infants took place between 8 and 14 years of age,[31] but unfortunately, bronchial reactivity was not measured.

The main strengths of the present study include a long follow-up from birth until 14 to 22 years of age and the use of birth weights adjusted for gestational age. The two study groups consisted of disproportionately grown twin pairs born at <38 gestational weeks; the twins had identical prenatal and postnatal environments, minimizing the effect of early confounding factors, like maternal smoking and genetic predisposition to asthma.[3,15] None of them had bronchopulmonary dysplasia in infancy nor asthma in later life. In addition, the subjects were studied by identical lung function and cold air challenge tests 6 years apart. The within-pair analyses used in the study further minimized the effect of early-life confounders, but did not allow the analysis of later outcome confounding or disease modifying factors like smoking or pubertal degree.

The main weakness of the study is the small number of patients; only 38 study subjects consisting of 19 twin pairs completed the follow-up. The collection of even this small group lasted for 8 years, expanding the age distribution of the study subjects. We checked afterwards the patient records at our hospital, and the total number of disproportionally grown twin pairs born at <38 weeks was 32 twin-pairs (64 subjects); thus, our follow-up until early adulthood covered 60% of all eligible study subjects. For comparison, the numbers of IUGR cases were only 122 and 55 in the two large epidemiological population studies though the designs were cross-sectional with no follow-up data available.[26,27]

In conclusion, some evidence was found in support of the Barker's hypothesis of intrauterine programming of later pulmonary morbidity. At the age of 14 to 22 years, lung function evaluated by FEV% and FEF25-75 was decreased and bronchial reactivity to cold air was increased in the twins with IUGR compared with their normally grown counterparts. As in the case of cardiovascular morbidity, the final effect of intrauterine programming, and thus the accuracy of Barker's hypothesis, might be assessed not earlier than in mid-adulthood.

Funding: None.
Ethical approval: Not needed.
Competing interest: No benefits in any form have been received or will be received from any commercial party related directly or indirectly to the subjects of this article.
Contributors: Nikolajev K collected and analyzed the data under the supervision of Korppi M. Koskela H provided advice in the aspects of lung function and cold air challenge tests. All authors contributed to the design and interpretation of the study and to the writing of the paper. Korppi M is the guarantor.

References

1 Barker DJ, Osmond C. Infant mortality, childhood nutrition, and ischaemic heart disease in England and Wales. Lancet 1986;1:1077-1081.
2 Barker DJ, Osmond C, Law CM. The intrauterine and early postnatal origins of cardiovascular disease and chronic bronchitis. J Epidemiol Community Health 1989;43:237-240.
3 Stick S. Pediatric origins of adult lung disease. 1. The contribution of airway development to paediatric and adult lung disease. Thorax 2000;55:587-594.
4 Gilliland FD, Berhane K, McConnell R, Gauderman WJ, Vora H, Rappaport EB, et al. Maternal smoking during pregnancy, environmental tobacco smoke exposure and childhood lung function. Thorax 2000;55:271-276.
5 Piippo-Savolainen E, Remes S, Kannisto S, Korhonen K, Korppi M. Early predictors for adult asthma and lung function abnormalities in infants hospitalized for bronchiolitis: a prospective 18- to 20-year follow-up. Allergy Asthma Proc 2006;27:341-349.
6 Hakulinen AL, Heinonen K, Länsimies E, Kiekara O. Pulmonary function and respiratory morbidity in school-age children born prematurely and ventilated for neonatal respiratory insufficiency. Pediatr Pulmonol 1990;8:226-232.
7 Koumbourlis AC, Motoyama EK, Mutich RL, Mallory GB, Walczak SA, Fertal K. Longitudinal follow-up of lung function from childhood to adolescence in prematurely born patients with neonatal chronic lung disease. Pediatr Pulmonol 1996;21:28-34.
8 Moss TJ. Respiratory consequences of preterm birth. Clin Exp Pharmacol Physiol 2006;33:280-284.
9 Matthes JW, Lewis PA, Davies DP, Bethel JA. Birth weight at term and lung function in adolescence: no evidence for a programmed effect. Arch Dis Child 1995;73:231-234.
10 Shaheen SO, Sterne JA, Tucker JS, Florey CD. Birth weight, childhood lower respiratory tract infection, and adult lung function. Thorax 1998;53:549-553.
11 Susser M, Levin B. Ordeals for the fetal programming hypothesis. The hypothesis largely survives one ordeal but not another. BMJ 1999;318:885-886.
12 Lum S, Hoo AF, Dezateux C, Goetz I, Wade A, DeRooy L, et al. The association between birthweight, sex, and airway function in infants of nonsmoking mothers. Am J Respir Crit Care Med 2001;164:2078-2084.
13 Hoo AF, Stocks J, Lum S, Wade AM, Castle RA, Costeloe KL, et al. Development of lung function in early life: influence of birth weight in infants of nonsmokers. Am J Respir Crit Care Med 2004;170:527-533.
14 Greenough A, Yuksel B, Cheeseman P. Effect of in utero growth retardation on lung function at follow-up of prematurely born infants. Eur Respir J 2004;24:731-733.
15 Dezateux C, Lum S, Hoo AF, Hawdon J, Costeloe K, Stocks J. Low birth weight for gestation and airway function in infancy:

exploring the fetal origins hypothesis. Thorax 2004;59:60-66.
16 Dwyer T, Morley R, Blizzard L. Twins and fetal origins hypothesis: within-pair analyses. Lancet 2002;359:2205-2206.
17 Nikolajev K, Heinonen K, Hakulinen A, Länsimies E. Effects of intrauterine growth retardation and prematurity on spirometric flow values and lung volumes at school age in twin pairs. Pediatr Pulmonol 1998;25:367-370.
18 Nikolajev K, Heinonen K, Koskela H, Korppi M, Länsimies E, Jokela V. Determinants of bronchial responsiveness at school age in prematurely born children. Pediatr Pulmonol 1999;28:408-413.
19 Nikolajev K, Korppi M, Remes K, Länsimies E, Jokela V, Heinonen K. Determinants of bronchial responsiveness to methacholine at school age in twin pairs. Pediatr Pulmonol 2002;33:167-173.
20 Pihkala J, Hakala T, Voutilainen P, Raivio K. Characteristic of recent fetal growth curves in Finland. Duodecim 1989;105:1540-1546.
21 Standardization of spirometry—1987 update. Statement of the American Thoracic Society. Am Rev Respir Dis 1987;136:1285-1298.
22 Solymar L, Aronsson PH, Bake B, Bjure J. Nitrogen single breath test, flow-volume curves and spirometry in healthy children, 7-18 years of age. Eur J Respir Dis 1980;61:275-286.
23 Koskela HO, Räsänen SH, Tukiainen HO. The diagnostic value of cold air hyperventilation in adults with suspected asthma. Respir Med 1997;91:470-478.
24 Bagchi S, Salihu HM. Birth weight discordance in multiple gestations: occurrence and outcomes. Review. J Obstet Gynaecol 2006;26:291-296.
25 Rona RJ, Gulliford MC, Chinn S. Effects of prematurity and intrauterine growth on respiratory health and lung function in childhood. BMJ 1993;306:817-820.
26 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.
27 Edwards CA, Osman LM, Godden DJ, Campbell DM, Douglas JG. Relationship between birth weight and adult lung function: controlling for maternal factors. Thorax 2003;58:1061-1065.
28 Laerum BN, Svanes C, Gulsvik A, Iversen M, Thorarinsdottir HR, Gislason T, et al. Is birth weight related to lung function and asthma symptoms in Nordic-Baltic adults? Respir Med 2004;98:611-618.
29 Canoy D, Pekkanen J, Elliott P, Pouta A, Laitinen J, Hartikainen AL, et al. Early growth and adult respiratory function in men and women followed from the fetal period to adulthood. Thorax 2007;62:396-402.
30 Orfei L, Strachan DP, Rudnicka AR, Wadsworth ME. Early influences on adult lung function in two national British cohorts. Arch Dis Child 2008;93:570-574.
31 Doyle LW, Chavasse R, Ford GW, Olinsky A, Davis NM, Callanan C. Changes in lung function between age 8 and 14 years in children with birth weight of less than 1501 g. Pediatr Pulmonol 1999;27:185-190.

Received April 9, 2008
Accepted after revision June 27, 2008