ORIGINAL ARTICLE

Growth and adrenal androgen status at 7 years in very low birth weight survivors with and without bronchopulmonary dysplasia

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Aims: To evaluate whether 7 year old VLBW (very low birth weight, <1500 g) survivors with and without bronchopulmonary dysplasia (BPD) evince similar growth status and higher adrenal androgen (AA) levels than term controls, and whether AA levels are higher in VLBW children born small for gestational age (SGA) than in non-SGA cases.

Methods: Assessment of height standard deviation score (SDs), body mass index (BMI), and serum androstenedione and dehydroepiandrosterone sulphate levels in 31 VLBW children with BPD, 33 without BPD (no-BPD group), and 33 term controls.

Results: Lower median (range) height SDs was found in BPD (−1.0 (−3.4 to 1.4) SD) and no-BPD (−0.9 (−2.9 to 2.2) SD) children than in term controls (0.3 (−1.5 to 1.9) SD). Low BMI (below 10th centile) was more common in both the BPD (18 (58%)) and no-BPD (16 (49%)) children compared to term cases (3 (9%)). The median (range) androstenedione levels tended to be higher in the BPD (0.8 (0 to 2.8) nmol/l) and no-BPD (0.8 (0 to 2.3) nmol/l) groups than in term controls (0.6 (0 to 1.8)). Higher median (range) dehydroepiandrosterone sulphate levels were detected in the no-BPD compared to the term group (0.9 (0 to 4.1) v 0.3 (0 to 2.3) μmol/l). VLBW children born SGA had higher AA levels compared to non-SGA cases.

Conclusions: At 7 years of age, VLBW children are shorter and tend to have higher AA levels than term controls, but VLBW children with and without BPD do not differ from each other in growth or AA status. Those born SGA have higher AA levels compared to non-SGA cases. The consequences of these findings to final height and to later metabolic and vascular health remain to be determined.

Poor long term growth has been reported in very low birth weight (VLBW) schoolchildren compared to children with normal birth weights.^{1–4} Some,⁵ albeit not all^{3,4,6} authors suggest that bronchopulmonary dysplasia (BPD) increases the risk of later growth impairment in VLBW children. However, most studies concerning the consequences of VLBW and BPD for growth date from the presurfactant era. Administration of prenatal corticosteroids and postnatal surfactants alleviate initial respiratory problems of VLBW infants and might be thought to facilitate better growth. On the other hand, surfactant therapy might have allowed particularly sick and vulnerable infants to survive. These might go on to show more growth impairment. Our first hypothesis was that BPD children born in the surfactant era do not differ from VLBW cases without BPD and term controls in growth at early school age.

Premature adrenarche refers to an early increase in adrenal androgen (AA) production. This often leads to the development of pubic hair (pubarche) before the age of 8 years in girls and 9 years in boys, with or without axillary hair and pubertal odour, independent of gonads or gonadotropins (see for review, Saenger and DiMartino-Nardi⁷). Furthermore, it may lead to an accelerated mid-childhood growth spurt,⁸ and thus affect catch-up growth and final height.^{9,10} According to clinical observations recorded by an experienced paediatric endocrinologist (HLL), VLBW children seem to be over-represented among cases with premature pubarche. Our second hypothesis was that VLBW children have higher AA levels at 7 years of age than term controls, and those with higher AA levels might evince faster catch-up growth.

An association has been suggested between intrauterine growth retardation and adrenarche in prematurely born children¹¹ and term born girls.¹⁰ However, published data on

adrenarche and growth of VLBW children born SGA are limited. Our third hypothesis was that AA levels would be higher in VLBW schoolchildren born SGA compared to non-SGA cases.

We aimed to test these three hypotheses in our study on height, catch-up growth, nutritional status, and AA levels in 7 year old VLBW children with and without BPD born in the surfactant era.

PATIENTS AND METHODS

The original cohort consisted of 242 VLBW infants (birth weight <1501 g) born in Tampere University Hospital during the years 1990–94, and has been described in detail elsewhere.¹² At 28 days' postnatal age, 59 of them had fulfilled the criteria for BPD (need for oxygen (O₂) supplementation and chest x ray findings typical of BPD,¹³ interpreted by a paediatric radiologist). Of the 50 surviving BPD cases, 47 could be traced at 7 years of age, and 34 gave consent to the study (BPD group). Two age and sex matched controls were selected for each BPD child: a VLBW child without BPD diagnosis at 28 days' postnatal age from the original cohort (no-BPD group) and the next-born non-SGA term child of the same sex (term group). In cases of refusal (nine VLBW and 20 term children), new controls were

Abbreviations: AA, adrenal androgen; BMI, body mass index; BPD, bronchopulmonary dysplasia; DHEAS, dehydroepiandrosterone sulphate; IVH, intraventricular haemorrhage; MUAC, middle upper arm circumference; O₂, oxygen; RDS, respiratory distress syndrome; SDs, standard deviation score; SES, socioeconomic status; SFT, skinfold thickness; SGA, small for gestational age; WHR, waist-to-hip ratio; VLBW, very low birth weight

selected according to the same principles. The main reasons for refusal were the child's health problems, distance from the hospital, or fear of the examinations. The children participated in a larger study on the outcome of VLBW children at early school age. In this report, we present results on their growth and adrenal androgen levels. Children with severe cerebral palsy (three BPD, one no-BPD, and one term) in whom height measurement was considered unreliable were excluded. Eventually, the BPD group comprised 31, the no-BPD group 33, and the term group 33 children. The BPD, no-BPD, and term children who refused had gestational ages and birth weights similar to those of the participants. The ethical committee of Tampere University Hospital approved the study. The parents gave informed written consent.

Perinatal and neonatal data were collected from medical records, covering the child's gestational age, birth weight, birth length, and head circumference at birth. Those with a birth weight more than 2 standard deviations (SD) below the Finnish mean for gestational age were considered small for gestational age (SGA).¹⁴ Administration of corticosteroids prenatally or postnatally before the first discharge from hospital, surfactant treatment as rescue therapy for respiratory distress syndrome (RDS), duration of ventilator therapy, both postnatal and corrected gestational age at O₂ withdrawal, and intraventricular haemorrhage grade III–IV¹⁵ were recorded.

Information on the child's health and family background was collected by a mailed questionnaire, and the answers corroborated at the examination visit. Physician diagnosed milk and/or cereal allergies and the use of inhaled corticosteroids were recorded. Socioeconomic status (SES) was determined according to the occupation of the parent with the most favourable SES.¹⁶ The parents' reported heights and weights were plotted against standardised Finnish growth curves.¹⁷ Midparental height ((mother's height (SD) + father's height (SD))/2) was calculated. Mother's age at menarche was categorised as "early" (<12 years), "average" (12–15 years), and "late" (≥15 years). Father's growth pattern was considered "early" if he had reached his final height before the age of 17–18 years, and "late" if thereafter.

The child's standing height was measured using a Harpenden stadiometer (Holtain Limited, UK), plotted against standardised Finnish growth curves,¹⁷ and height standard deviation score (height SDs, deviation of height in SD units from the mean height for age and sex) was recorded. Height SDs of less than −1.2 SD (lowest quartile in this population) was considered low. The child's catch-up growth was considered incomplete if her/his height SDs at 7 years of age was more than 1.5 SD below the midparental height. Each child was weighed in underwear with a digital scale (Seca 707, Germany). Body mass index (BMI), the ratio of weight (kg) and squared height (m²), was calculated. BMIs below the 10th centile of Finnish reference values were considered low, and above the 90th centile high.¹⁸ Waist, hip, and middle upper arm circumferences (MUAC) were measured with a plastic tape measure, and waist-to-hip ratios (WHR) computed. The biceps, triceps, subscapular, and suprailiacal skinfold thicknesses (SFT) were measured as previously described¹⁹ with a Harpenden skinfold calliper and expressed as means of three successive measurements, allowing for a 20% variation between the lowest and highest value. Pubertal status was staged according to Tanner.²⁰

A radiograph of the child's left wrist and hand was taken, using appropriate shields for stray radiation. The skeletal ages were determined by an experienced paediatric endocrinologist, blinded to the children's perinatal characteristics, according to the standards of Greulich and Pyle.²¹ Radioimmunoassays were used in the determination of androstenedione (Diagnostic Systems Laboratories, Inc.,

Webster, Texas, USA) and dehydroepiandrosterone sulphate (DHEAS) (DiaSorin Biomedica SpA, Saluggia, Italy) concentrations. The intra-assay coefficients of variation were 5.7% at 1.9 nmol/l and 4.0% at 5.8 nmol/l for androstenedione and 9.4% at 0.4 µmol/l and 3.9% at 4.0 µmol/l for DHEAS, and the detection limits 0.3 nmol/l and 0.1 µmol/l, respectively. Proportions were computed for hormone levels exceeding the highest quartile in this material (1.0 nmol/l for androstenedione and 1.1 µmol/l for DHEAS) and for levels exceeding the upper prepubertal limits in our laboratory (2.5 nmol/l and 1.6 µmol/l, respectively).

Statistical methods

One way analysis of variance (ANOVA) with Bonferroni correction was used for normally distributed variables, the Kruskal-Wallis test for variables with non-normal distribution, and the χ^2 test for categorical variables in the three-group comparisons (BPD–no-BPD–term and SGA–non-SGA–term). Differences between two groups were analysed by the Mann-Whitney U test, the χ^2 test, or Fisher's exact test with a p value adjustment for multiple comparisons when appropriate.

Risk factors for low height SDs (lowest quartile in this material), low BMI (below 10th centile),¹⁸ and AA levels in the highest quartile in this material were evaluated using forward stepwise logistic regression analysis. Independent variables were tested in four categories: (A) prenatal corticosteroid therapy (no/yes), midparental height (SD), the parents' BMIs (kg/m²); (B) gestational age (full weeks), birth weight (g), SGA status (no/yes), gender; (C) IVH gr III–IV (no/yes), postnatal corticosteroid therapy before first discharge (no/yes), BPD (no/yes), corrected gestational age at O₂ therapy withdrawal (wk); and (D) SES, inhaled corticosteroid therapy after first discharge (no/yes). A combined model was formed from the significant factors in each category. All categories were tested in the VLBW population, and category D in the whole study population. The limit for significance was set at 0.05 to enter and 0.10 to remove in the logistic regression analysis, and the results expressed as odds ratios (OR) and 95% confidence intervals (95% CI). Statistical significance was defined as p < 0.05 (two sided). SPSS version 10.1 was used in the analyses.

RESULTS

Table 1 shows the perinatal and neonatal features of the VLBW children with and without BPD. Compared to the no-BPD group, the BPD children had been smaller and more premature at birth, less frequently SGA, received more often postnatal corticosteroids, and needed longer O₂ and ventilator therapy (table 1). One child in the no-BPD group had undergone open ventriculostomy neonatally due to hydrocephalus. The term control group had a mean (SD) gestational age of 40 (1) weeks and birth weight of 3614 (481) grams.

Former milk and/or cereal allergy was reported in one BPD, two no-BPD, and two term cases. No currently symptomatic significant food allergies were reported. After the first discharge, 10 (32%) BPD, 6 (18%) no-BPD, and 2 (6%) term children had received daily inhaled corticosteroids for several months; the difference between the BPD and term group was significant (p < 0.05). The groups did not differ with respect to SES, parental growth characteristics, or mothers' menarche. In all groups, the mothers' reported mean heights ranged from 164 to 166 cm and mean weights from 64 to 66 kg, the fathers' mean heights from 178 to 180 cm and mean weights from 83 to 86 kg, and the median midparental heights from −0.20 to 0.15 SD.

Table 1 Perinatal and neonatal characteristics of the very low birth weight children during the first hospitalisation

	BPD group n = 31	No-BPD group n = 33
Gestational age (wk)	27 (2) [23–30]*	29 (2) [25–35]
Birth weight (g)	954 (201) [570–1300]†	1127 (236) [605–1490]
Birth length (cm)	35 (3) [30–40]†	37 (3) [30–41]
Head circumference at birth (cm)	25 (2) [21–28]*	27 (2) [21–31]
Male	19 (61%)	21 (63%)
SGA	5 (16%)‡	14 (42%)
Prenatal corticosteroids	10 (32%)	13 (39%)
Postnatal corticosteroids	17 (55%)*	4 (12%)
Surfactant	14 (45%)	8 (24%)
Ventilator therapy	29 (94%)†	22 (67%)
Duration (days), median (range)	26 (0–89)†	2 (0–44)
O ₂ supplementation	31 (100%)	31 (94%)
Duration (days), median (range)	61 (29–127)†	23 (0–86)
Corrected gestational age at O ₂ withdrawal (wk)	36 (4) [31–45]*	32 (2) [28–38]
IVH (grade III–IV)	8 (26%)‡	2 (6%)

Values are expressed as mean (SD) [range] or n (%) unless indicated otherwise. SGA, small for gestational age; O₂, oxygen; IVH, intraventricular haemorrhage.

*p<0.001, compared to no-BPD group; †p<0.01, compared to no-BPD group; ‡p<0.05, compared to no-BPD group.

Growth characteristics

Table 2 shows anthropometric data at 7 years in the BPD, no-BPD, and term groups. Both VLBW groups were significantly shorter than the term group ($p < 0.01$) but there was no difference in height status, percentage with low height SDs, or frequency of incomplete catch-up growth between the BPD and no-BPD groups. However the BPD group had lower BMI and MUAC than the term group.

The differences between chronological and skeletal ages were similar in the BPD, no-BPD, and term groups, and they did not differ in the comparison between VLBW children born SGA and non-SGA. Among VLBW children, no difference was found between the SGA and non-SGA cases in the median height SDs, BMI, WHR, MUAC, or SFTs (data not shown). The frequency of low height SDs was 10 (53%) in the SGA and 12 (32%) in the non-SGA group.

All children were prepubertal according to Tanner staging. Only one SGA girl in the no-BPD group had comedos and sweat odour in connection with increased AA levels.

Adrenal androgens at 7 years

Compared to term controls, both the BPD and no-BPD children tended to have higher androstenedione levels, and the no-BPD group had higher DHEAS (table 3). Androstenedione levels >1.0 nmol/l were more common in the no-BPD than the term group. In only one BPD child did androstenedione concentration exceed 2.5 nmol/l. DHEAS levels >1.1 μ mol/l were significantly more common in both the BPD and no-BPD cases than in term controls. VLBW cases with incomplete catch-up growth had lower median (range) androstenedione levels than those who had completed it (0.4 (0–1.8) versus 0.9 (0–2.8) nmol/l, $p < 0.05$), but no significant difference was found in DHEAS.

VLBW children born SGA had higher androstenedione and DHEAS levels than the non-SGA cases and term controls (table 3). In addition, non-SGA children tended to have DHEAS >1.1 μ mol/l more often than term controls.

Skeletal ages tended to lag behind chronological ages significantly more among VLBW children with androstenedione levels ≤ 1.0 nmol/l ($n = 38$) than among those with levels >1.0 nmol/l ($n = 18$), the median (range) differences (chronological age – skeletal age) being 0.6 (–0.9 to 1.9) and 0.1 (–1.4 to 1.5) years, respectively ($p = 0.06$). These groups had median (mean) [range] skeletal ages of 6.5 (6.6) [5.5–8.0] and 7.3 (7.1) [5.3–9.0] years, respectively.

Risk factor analysis of growth and androgen status

Among VLBW children, the probability of short stature at 7 years of age appeared to be decreased by higher midparental height (OR 0.01, 95% CI 0.00 to 0.11), and increased in SGA children (OR 73.2, 95% CI 3.7 to 1432) and in connection with higher corrected gestational age at O₂ therapy withdrawal (OR 1.30, 95% CI 1.02 to 1.66). Mother's high BMI seemed to protect from low BMI (OR 0.86, 95% CI 0.74 to 0.99). Being born SGA appeared to predict AA levels in the highest quartile (OR 3.33, 95% CI 1.03 to 10.7). No significant risk factors emerged for any of the analysed parameters in the whole study population.

DISCUSSION

Anthropometric evaluation at 7 years of age showed that VLBW children were shorter than term controls. BPD diagnosed at 28 days' postnatal age did not appear as a determining factor in the short stature among VLBW children. Children with BPD were thinner than term controls, but did not differ from the no-BPD group in this respect. Supporting our hypothesis, VLBW children had higher AA levels at 7 years of age compared to term controls, and higher

Table 2 Anthropometric data on the children at the examination visit

	BPD n = 31	No-BPD n = 33	Term n = 33	p
Age (y)	7.2 (6.7–7.8)	7.3 (6.9–8.1)	7.3 (6.9–8.3)	0.247
Skeletal age (y), mean (SD) [range]	6.7 (0.7) [5.3–8.0]	6.8 (0.8) [5.5–9.0]	6.7 (0.8) [5.0–8.3]	0.732
Height (cm), mean (SD) [range]	119.4 (6.6) [107.0–130.3]*	120.7 (6.2) [110.0–134.7]†	124.9 (4.7) [115.3–134.5]	0.001
Height SDs (SD)	–1.0 (–3.4–1.4)*	–0.9 (–2.9–2.2)*	0.3 (–1.5–1.9)	<0.001
Weight (kg), mean (SD) [range]	21.2 (4.1) [15.0–32.5]*	22.0 (4.2) [16.2–32.0]*	25.2 (4.1) [20.4–36.1]	<0.001
BMI (kg/m ²), mean (SD) [range]	14.8 (1.7) [12.8–20.1]†	15.0 (1.9) [12.4–20.5]	16.1 (2.1) [13.4–21.5]	0.015
<10th centile	18 (58%)*	16 (49%)*	3 (9%)	<0.001
>90th centile	3 (10%)	3 (9%)	7 (21%)	0.268
MUAC (cm)	17.0 (15.0–22.5)†	17.1 (15.1–22.0)	18.4 (16.1–23.6)	0.021
WHR, mean (SD) [range]	0.88 (0.07) [0.58–0.96]	0.87 (0.06) [0.63–0.98]	0.87 (0.03) [0.79–0.92]	0.779
Biceps SFT	4.2 (2.1–7.7)	3.6 (2.0–7.3)	4.0 (1.9–9.4)	0.184
Triceps SFT	6.4 (3.3–10.8)	6.1 (2.9–9.3)	6.6 (4.2–12.6)	0.508
Subscapular SFT	4.8 (3.4–8.9)	4.6 (3.1–9.8)	5.2 (4.1–7.7)	0.224
Suprailiacal SFT	3.8 (2.2–6.8)	3.2 (2.5–9.3)‡	3.8 (2.8–8.9)	0.043

Values are expressed as median (range) or n (%) unless indicated otherwise. SDs, standard deviation score; BMI, body mass index; MUAC, middle upper arm circumference; WHR, waist-to-hip ratio; SFT, skinfold thickness.

*p<0.01, compared to term group; †p<0.05, compared to term group; ‡p=0.08, compared to term group.

Table 3 Serum hormone levels of the VLBW children, grouped according to BPD and SGA status, and term controls

	BPD n=26	No-BPD n=32	SGA n=18	Non-SGA n=40	Term n=32	p ¹	p ²
Androstenedione (nmol/l)	0.8 (0–2.8)*	0.8 (0–2.3)*	1.2 (0–2.8)†‡	0.7 (0–1.8)	0.6 (0–1.4)	0.029	0.003
>1.0 nmol/l	8 (31%)	11 (34%)‡	10 (56%)‡§	9 (23%)	3 (9%)	0.045	0.001
DHEAS (µmol/l)	0.5 (0–5.8)	0.9 (0–4.1)‡	1.2 (0.2–5.8)‡§	0.4 (0–2.5)	0.3 (0–2.3)	0.070	0.001
>1.1 µmol/l	9 (35%)‡	11 (34%)‡	9 (50%)‡	11 (28%)¶	2 (6%)	0.012	0.002
>1.6 µmol/l	6 (23%)	5 (16%)	6 (33%)‡	5 (13%)	2 (6%)	0.185	0.029

Values are expressed as median (range) or n (%). DHEAS, dehydroepiandrosterone sulphate.

p¹, comparison BPD v no-BPD v term; p², comparison SGA v non-SGA v term; *p=0.07, compared to term group; †p=0.07, compared to non-SGA group; ‡p<0.05, compared to term group; §p<0.05, compared to non-SGA group; ¶p=0.06, compared to term group.

AA levels seemed to be associated with faster catch-up growth. As expected, AA levels were higher in VLBW children born SGA than in the non-SGA cases.

The reliability of anthropometric data is an important aspect in growth evaluation. It was decided to use SGA criteria based on Finnish reference values for birth weight because birth length measurement carries several risks of bias: the head may be reshaped shortly after delivery, and especially premature babies may be too fragile for the procedure. Parental height and weight values were obtained by interview, this information being thus less accurate than if they had been measured. However, Finnish parents should be well aware of their measurements because mothers are measured and weighed at maternity clinics and fathers during recruitment procedures.

As in reports from the presurfactant era,^{1–3} our VLBW children, born after the introduction of surfactant treatment, seemed to grow less well than term controls. No significant difference in height or BMI was found between VLBW children with and without BPD. However, it is possible that the most seriously impaired children at risk of poor growth did not participate. Assessment of the exact role of BPD in growth impairment is difficult because several other neonatal conditions possibly affecting growth had also been more frequent in VLBW children with BPD than in those without.⁶ At 7 years of age, a significant association was found in our VLBW children between low height SDs and corrected gestational age at O₂ therapy withdrawal. This finding suggests that the severity of lung disease that develops during the neonatal period might influence future growth. Children with prolonged neonatal respiratory problems may also later have repeated infections and respiratory symptoms, and need inhaled corticosteroids (as in the present material)—all conceivable risk factors for impaired growth. Possible differences in dietary habits of the groups remain undetermined here. However, the frequencies of diagnosed food allergies were similar in all groups. Further research is needed to evaluate whether interventions, including adequate follow up and management of respiratory symptoms and nutritional counselling, improve growth and nutritional status of VLBW children.

Furthermore, parental growth characteristics (obtained by interview) appeared as predictors of short stature and low BMI in VLBW children at 7 years of age. In term children, target height has previously been reported to affect the growth pattern in childhood,²² and mother's BMI has been suggested at least in part to explain the association between birth weight and adult body mass index.²³

Compared to children born normal size, term born SGA children have been reported to run a higher risk of also being short later in life,^{24–25} although most of them show catch-up growth at early ages.⁹ The comparability of the studies is restricted due to differences in criteria for SGA status. In one report, VLBW children born SGA did not grow well in infancy, but at 5 years of age did not present with poorer growth compared to non-SGA cases with similar birth weights but shorter gestation.²⁶

Both premature¹¹ and term¹⁰ SGA children have been proposed to present with earlier adrenarche than non-SGA cases, linked with both prenatal and postnatal weight gain.¹¹ Our VLBW children born SGA had higher AA levels but similar heights at 7 years of age compared to the non-SGA cases. Furthermore, those with higher androstenedione levels seemed to have less risk of incomplete catch-up growth at 7 years of age. These findings suggest that also among VLBW children, higher AA levels might influence catch-up growth by accelerating mid-childhood growth.⁸ In our study population, the skeletal ages were in accord with chronological ages, but tended to be more advanced in children with androstenedione levels >1.0 nmol/l compared to the rest of the VLBW cases. The impact of higher AA levels and possibly accelerated catch-up growth on final height remains to be determined. Previous reports on the association of adrenarche and final height are controversial.^{8–10}

Premature adrenarche was long held to be a benign, normal variant of puberty. However, children with premature adrenarche may be at risk of subsequent insulin resistance and associated complications, such as diabetes mellitus, dyslipidaemia, and cardiovascular disease.^{27–28} In addition, premature pubarche may precede ovarian hyperandrogenism in girls.²⁹ Also in this respect, follow up of growth and adrenarche of VLBW children may have long term value, for example in terms of early dietary counselling.

Conclusions

VLBW children born in the surfactant era, regardless of BPD, seem to be shorter than term controls at early school age. Interventions are needed to improve growth and poor nutritional status among VLBW children.

Our results also suggest that adrenal puberty may be more florid in VLBW survivors, especially in those born SGA, possibly leading to accelerated catch-up growth and reduced final height. The present data can be of value in the long term follow up of these children, particularly with regard to the development of metabolic and vascular disease later in life.

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The course of wheezing

In a New Zealand birth cohort study (Malcolm R Spears and colleagues. *New England Journal of Medicine* 2003;**349**:1414–22, see also editorial, *ibid*: 1473–5) almost three quarters of the subjects (72.6%) had significant wheezing at some time in childhood and more than a third (37%) of these (27% of the cohort) wheezed as young adults. Impairment of lung function in persistent wheezers dated from before the age of 9 years and did not get worse by early adult life.

A total of 1139 children were born in Dunedin between April 1972 and March 1973 and still lived in the province of Otago when they were 3 years old. Of these children 1037 entered the study as 3-year-olds and complete study data to the age of 26 years was obtained for 613. They were followed up every 2 years to age 15 and at ages 18, 21, and 26 years. Data from questionnaires and from tests of lung function, bronchial responsiveness, and allergy were collected from the age of 9 years.

By the age of 26 years only 168 of the 613 subjects (27%) had never reported wheezing that occurred more than once or twice a year and lasted more than an hour. Half (315 of 613) had reported wheezing on two or more visits. Wheezing was persistent from onset in childhood to age 26 in 89 (14.5%). It had remitted in 168 (27%) but subsequently relapsed in 76 (12.4% of the analysed cohort, 45% of remitters). Between the ages of 9 and 26 the line of the graph of FEV₁: FVC for persistent wheezers remained parallel to but below that for nonwheezers. Factors associated with wheezing at age 26 years (persistence or relapse) were female sex, house dust mite sensitisation, bronchial hyperreactivity, and smoking at age 21 years. Early age of onset was associated with higher risk of relapse, each year of delay in onset reducing the risk of relapse by 11%. Relapse after the age of 26 is thought to be uncommon.

Wheezing in childhood is common but about two thirds of children who ever wheeze no longer do so as young adults. Persistent wheezers already have impaired lung function at age 9 years but the degree of impairment does not increase. The origins of asthma are in early childhood.