First- and Second-Trimester Fetal Size and Asthma Outcomes at Age 10 Years

Steve Turner[1], Nanda Prabhu[1], Peter Danielian[2], Geraldine McNeill[3], Leone Craig[3], Keith Allan[4], Rebecca Cutts[1], Peter Helms[1], Anthony Seaton[4], and Graham Devereux[1,4]

[1]Academic Child Health, [2]Obstetrics and Gynaecology, [3]Public Health Nutrition Research Group, and [4]Environmental and Occupational Medicine, University of Aberdeen, United Kingdom

***Rationale*: Greater early fetal size is associated with reduced asthma risk and improved lung function in early childhood.**

***Objectives*: To test the hypothesis that associations between early fetal size, asthma symptoms, and lung function persist into later childhood.**

***Methods*: In a longitudinal study, first- and second-trimester fetal measurements were recorded. At 10 years of age a respiratory questionnaire was completed. Spirometry, bronchial challenge, and skin prick testing were undertaken in a subset.**

***Measurements and Main Results*: Fetal measurements were available in the first trimester for 853 individuals and the second trimester for 1,453. Questionnaires were returned for 927 children and 449 underwent detailed phenotyping. For each millimeter increase in first-trimester size, asthma risk reduced by 6% (95% confidence interval [CI], 1–11) and FEV_1 was higher by an average of 6 ml (95% CI, 1–11). First-trimester size was reduced in those with asthma at both 5 and 10 years compared with early or late onset wheeze ($P < 0.02$). Compared with persistent high growth in first and second trimesters, persistent low growth was associated with increased asthma risk (odds ratio, 2.8; 95% CI, 1.2–6.9) and a mean reduction in FEV_1 of 103 ml (95% CI, 13–194), whereas increasing fetal size was associated with increased eczema risk (odds ratio, 2.5; 95% CI, 1.2–5.3).**

***Conclusions*: Reduced fetal size from the first trimester is associated with increased risk for asthma and obstructed lung function in childhood. Relative change in size after the first trimester is associated with eczema.**

Keywords: asthma; child; fetus; longitudinal study

The associations between reduced fetal size at birth, asthma (1), and reduced lung function (2–4) in adulthood suggest that antenatal factors determine asthma risk many years after delivery. Several antenatal exposures have now been associated with reduced fetal size and childhood asthma (5–7). For example, pregnant women who smoke (5), whose diet is insufficient in certain nutrients (6), and who have complications of pregnancy (7) are at risk of delivering smaller infants at increased risk for asthma in childhood. Understanding when the relationship between fetal size and asthma outcomes is established will give insight into asthma etiology and be relevant to intervention studies aimed at asthma prevention.

Recently two groups, including ours, have described an apparent protective effect of longer first- and second-trimester fetal size on the development of asthma symptoms at 3 (8) and 5 (9) years of age. Reduced first-trimester maternal plasma α-tocopherol (9) and maternal smoking beyond the second trimester (5) are associated with reduced fetal size in the first and second trimesters, respectively, and may be relevant to the underlying mechanism. These studies provide insight into when critical exposures might be occurring in the context of asthma pathogenesis but are limited in their relatively short follow-up because asthma symptoms in 3 and 5 year olds can be transient in some individuals and many children develop asthma after 5 years of age (10).

The 10-year follow-up of our birth cohort is now complete and here we test the hypothesis that longer early fetal size is associated with reduced asthma and increased FEV_1 in 10-year-olds.

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Longer first-trimester fetal size is known to be associated with increased risk for asthma in early childhood.

What This Study Adds to the Field

The relationship between longer fetal size in the first trimester and childhood asthma symptoms persists to age 10 years. In contrast, eczema and hay fever are associated with changes in fetal size after the first trimester.

METHODS

Study Design

A birth cohort study was recruited between 1997 and 1999. First- and second-trimester fetal measurements were collected. At age 10 years a postal respiratory questionnaire (International Study of Asthma and Allergy in Children [11]) was completed and participants were invited to attend for a detailed clinical assessment. The study was approved by the North of Scotland Research Ethics Committee, written parental consent was obtained, and children gave verbal assent.

Recruitment

Mothers attending an antenatal clinic were invited to enroll in a longitudinal cohort study designed to relate maternal dietary exposures to childhood asthma. There was no prior selection for parental asthma or allergy. Fuller details of recruitment have been presented elsewhere (12). Mothers who agreed to participate completed a detailed questionnaire from which details of maternal smoking and asthma were obtained.

(*Received in original form December 24, 2010; accepted in final form May 26, 2011*)

Supported by the Medical Research Council and Tenovus Scotland.

Author contributions: S.T., N.P., and G.D. conceived the idea and wrote the manuscript; conception and design, S.T., N.P., G.D., and A.S.; analysis and interpretation, S.T., G.D., A.S., and G.Mc.N.; drafting the manuscript for important intellectual content, S.T., G.D., and A.S.; data collection, N.P., K.A., and R.C. All authors contributed to the maintenance of the birth cohort and paper.

Correspondence and requests for reprints should be addressed to Steve Turner, M.B.B.S., M.R.C.P., Department of Child Health, University of Aberdeen, Royal Aberdeen Children's Hospital, Foresterhill, Aberdeen AB25 2ZG, UK. E-mail: s.w.turner@abdn.ac.uk

This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org

Am J Respir Crit Care Med Vol 184. pp 407–413, 2011
Originally Published in Press as DOI: 10.1164/rccm.201012-2075OC on June 3, 2011
Internet address: www.atsjournals.org

Fetal Measurements

These were obtained as part of routine antenatal care in our institution. The first-trimester measurement was crown rump length (CRL) and second-trimester measurements were femur length (FL) and biparietal diameter (BPD). The fetal and neonatal measurements were expressed as raw data and z scores using published equations (13–16). The interobserver coefficient of variation for CRL measurements is between 8% and 10% (17). Additional detail on the method for making these measurements is provided in the online supplement.

Assessment at Age 10 Years

A postal questionnaire that included questions used for the 5-year follow-up of this cohort was used. Active asthma was defined as doctor-diagnosed asthma plus wheeze in the previous 12 months. Asthma medications was defined as an affirmative response to the question "has your child been prescribed medicines/inhalers for asthma in the last 12 months?". Participants were invited to attend the hospital for a detailed assessment. First, exhaled nitric oxide was measured using an on-line chemiluminescence analyzer (NIOX; Aerocrine, Solna, Sweden) in accordance with international recommendations (18). Spirometry was measured using a pneumotachograph (21/20; Vitalograph, Bucks, UK) with incentive software (Spirotrac IV version 4.22; Vitalograph) and application of standard quality control (19). An inhaled methacholine challenge was completed and additional detail on the method for making this measurement is provided in the online supplement. A methacholine dose–response slope was calculated; a higher dose–response ratio (DRR) indicates increased reactivity. The skin prick test was used to determine reactivity to common allergens (house dust mite, cat, dog, grass, egg, and peanut; ALK Abello, Northampton, UK). Positive and negative controls were used and atopy was defined as a weal greater than or equal to 3 mm to any allergen.

Statistics

The chi-square test and Student *t* test were used where appropriate to determine differences between the individuals who were enrolled who did and did not participate in the 10-year follow-up. As previously (9), results are presented with and without inclusion of individuals with low birth weight who are at risk of reduced lung function (20). Individuals were dichotomized about the median z score for fetal measurement and placed into one of four resulting groups: (*1*) persistent high growth (e.g., high CRL and BPD); (*2*) growth deceleration (e.g., high CRL and low BPD); (*3*) growth acceleration (e.g., low CRL and high BPD); and (*4*) persistent low growth (e.g., low CRL and BPD). Logistic regression models were used to relate fetal size and relative change in fetal size to respiratory symptoms and atopy adjusting for the same covariates used previously (9) and listed in the legends for relevant tables. Multivariate linear regression models were created to relate fetal size and relative change in fetal size to spirometry, log transformed FE_{NO}, and methacholine DRR adjusting for covariates previously considered (9) and listed in the legends for relevant tables. Repeated measures analysis was used to determine differences in % FEV_1 at ages 5 and 10 years between groups defined by CRL quartiles while adjusting for maternal smoking, maternal asthma, and Scottish Index of Multiple Deprivations (an index of socioeconomic status). Standard statistical software was used (SPSS version 18; IBM, Chicago, IL) and significance was assumed at P less than 0.05.

RESULTS

Participants

There were 1,924 live-born singletons of whom 1,840 were born in Aberdeen, United Kingdom, and birth weight recorded (including 97 with low birth weight). Among those with normal birth weight (i.e., $\geq$ 2.5 kg), CRL was recorded in 853, BPD in 1,453, and FL in 1,437. Asthma symptom questionnaires were returned by 927 individuals of whom 449 attended for clinical assessment. Table 1 compares outcomes for the whole study population with the 204 individuals in whom CRL was determined in the first trimester and FEV_1 determined at 10 years of age; the subset was enriched with individuals whose mothers did not smoke and who were larger in the second trimester.

Asthma Outcomes and Fetal Size

For each millimeter increase in first-trimester size, there was a 6% reduction in risk for asthma in the previous 12 months (95% confidence interval [CI], 1–11; $P = 0.03$) and a 6% reduction in risk for wheeze in the previous 12 months (95% CI, 0–11; $P = 0.04$) (Table 2). For each millimeter increase in CRL, FEV_1 was higher by an average of 6 ml (95% CI, 1–11; $P = 0.03$) and FVC by 6 ml (95% CI, 1–11; $P = 0.03$). For each millimeter increase in second-trimester size (BPD), there was a 13% reduction in risk for active asthma (95% CI, 1–23; $P = 0.04$). For each millimeter increase in BPD, there were increases in FEV_1 ($P = 0.001$); FVC ($P = 0.003$); and forced expiratory flow, midexpiratory phase ($P = 0.02$) (Table 2). There were no associations between FL and outcomes. An increase of one CRL z score was associated with a mean increase in % FEV_1 of 1.8 (95% CI, 0.3–3.5; $P = 0.03$) and an increase of one BPD z score was associated with a mean increase in % FVC of 3.4 (95% CI, 0.2–6.6; $P = 0.04$).

There were no associations between first- or second-trimester fetal measurement and atopy, methacholine DRR, or FE_{NO}. An interaction was sought between sex and fetal measurement for asthma outcomes at age 10 years; the impact between fetal measurements and asthma outcomes was similar for males and females. Table E1 in the online supplement presents results for the whole cohort (i.e., including low birth weight); the results were not substantially different from the results in Table 2. At birth, crown heel length and birth weight (but not occipitofrontal circumference) were positively associated with FEV_1 and FVC and there was a trend ($P = 0.06$) for reduced crown heel length to be associated with increased risk for receipt of asthma medications at age 11 years (*see* Table E2). The relationship between FEV_1 and crown heel length was nonsignificant ($P = 0.10$) when CRL ($P = 0.03$) was introduced to the model. Relationships between FEV_1 and birth weight and FVC and crown heel length and birth weight remained significant when CRL was also considered; in these models CRL was also significantly related to lung function.

Asthma Outcomes and Relative Change in Fetal Size

CRL and BPD. These results are presented in Table 3. Those with persistent low growth were at increased risk for diagnosed asthma ($P = 0.02$) and active asthma ($P = 0.01$) and also had reduced FEV_1 and FVC ($P < 0.03$) compared with those with persistent high growth. Those with persistent high growth had a mean increased % FEV_1 of 4.5 (95% CI, 0.2–8.8; $P = 0.04$) and % FVC of 8 (95% CI 0–8.0; $P = 0.05$) compared with those with persistent low growth. Those with growth deceleration were at reduced risk for hay fever ($P = 0.03$) and had reduced FVC ($P = 0.04$) compared with the reference group. Those with growth acceleration had increased risk for active asthma ($P = 0.02$) and eczema ($P = 0.01$).

CRL and FL. These results are presented in Table E3. Persistent low growth was associated with increased risk for asthma (odds ratio [OR], 4.9; 95% CI, 1.8–13.5; $P = 0.002$) and receipt of asthma medications in the last year (OR, 4.3; 95% CI, 1.5–12.8; $P = 0.009$) when compared with persistent high growth. Growth acceleration was associated with increased asthma (OR, 4.2; 95% CI, 1.3–13.9; $P = 0.02$), receipt of asthma medications (OR, 4.5; 95% CI, 1.3–16.2; $P = 0.02$), increased eczema (OR, 2.3; 95% CI, 1–5.3; $P = 0.04$), and reduced FEV_1

TABLE 1. COMPARISON OF OUTCOMES BETWEEN INDIVIDUALS WHERE MEASUREMENTS OF CROWN–RUMP LENGTH AT 10-WEEK GESTATION AND FEV_1 AT 10 YEARS OF AGE WERE BOTH AVAILABLE AND THE WHOLE COHORT

	Both CRL and FEV_1 Measured ($n = 204$)	Whole Cohort
Male sex	47% (96/204)	51% (912/1,797)
Maternal smoking during pregnancy	16% (33/204)*	30% (593/1,999)
History of maternal asthma	14% (28/204)	17% (334/1,999)
Mean CRL (SD), mm	45 (13), n = 204	44 (13), n = 903
Mean CRL length z-score	0.71	0.72
Mean biparietal diameter (SD), mm	48 (3), n = 192	48 (3), n = 1,560
Mean biparietal diameter z-score	0.60†	0.43
Mean femur length (SD), mm	33 (3), n = 188	33 (3), n = 1,544
Mean femur length z-score	0.71‡	0.56
Median gestation at term (range), wk	40 (35–42)	40 (26–42)
Mean birth weight (SD), g	3541 (467)	3,502 (476) n = 1,743
Ever wheeze at 10 yr	23% (47/203)	17% (205/926)
Wheeze in the last 12 mo aged 5 yr	13% (21/162)	15% (190/1,252)
Wheeze in the last 12 mo aged 10 yr	13% (26/202)	12% (110/925)
Doctor-confirmed asthma aged 10 yr	15% (30/203)	15% (136/927)
Asthma and wheeze in last 12 mo aged 10 yr	10% (21/203)	8% (78/924)
Prescribed asthma medications in last 12 mo aged 10 yr	13% (27/203)	12% (109/928)
Eczema at 10 yr	28% (55/199)	27% (247/918)
Hay fever at 10 yr	13% (26/198)	13% (121/904)
Atopic aged 10 yr	39% (77/196)	38% (165/433)
Mean % FEV_1 (SD) aged 5 years	103% (10) n = 107	103% (13) n = 447
Mean % FEV_1 (SD) aged 10 years	96% (12) n = 204	96% (12) n = 433
Living with an adult who smokes aged 10 years	9% (19/204)	10% (96/931)

Definition of abbreviation: CRL = crown–rump length.
* $P < 0.001$, † $P = 0.02$, and ‡ $P = 0.04$ compared with whole cohort, all other comparisons were not statistically different.

(mean reduction 153 ml; 95% CI, 2–304; $P = 0.05$) compared with persistent high growth.

Second- and third-trimester growth (BPD and birth weight). These results are presented in Table E4 of the online supplement. Persistent low growth was associated with reduced FEV_1 and FVC ($P \leqslant 0.01$) but not altered risk for symptoms and growth acceleration was associated with reduced FEV_1 and FVC ($P \leqslant 0.006$) and increased active asthma ($P = 0.04$).

TABLE 2. REGRESSION COEFFICIENTS AND 95% CONFIDENCE INTERVALS FOR RESPIRATORY SYMPTOMS AND PHYSIOLOGIC MEASUREMENTS AT 10 YEARS OF AGE FOR EACH MILLIMETER INCREASE IN FIRST- AND SECOND-TRIMESTER FETAL MEASUREMENT

	Crown Rump Length (*first trimester, n = 350 unless stated*)			Biparietal Diameter (*second trimester, n = 584 unless stated*)			Femur Length (*second trimester, n = 574 unless stated*)		
	Effect Size	95% CI	*P* Value	Effect Size	95% CI	*P* Value	Effect Size	95% CI	*P* Value
Odds ratio for diagnosed asthma	0.94	0.89 to 0.99	0.03	0.91	0.83 to 1.01	0.08	0.94	0.84 to 1.06	0.31
Odds ratio for active asthma	0.91	0.87 to 0.98	0.02	0.87	0.77 to 0.99	0.04	0.90	0.78 to 1.03	0.12
Odds ratio for asthma medications	0.94	0.88 to 0.99	0.03	0.90	0.81 to 1.00	0.05	0.95	0.84 to 1.07	0.38
Odds ratio for wheeze ever	0.97	0.93 to 1.02	0.20	0.99	0.91 to 10.7	0.75	0.97	0.88 to 1.06	0.49
Odds ratio for wheeze last 12 mo	0.94	0.89 to 1.00	0.04	0.93	0.84 to 1.03	0.17	0.95	0.84 to 1.06	0.34
Odds ratio for wheeze in last 12 mo and BHR	0.84	0.68 to 1.02	0.08 n = 111	0.87	0.69 to 1.11	0.27 n = 182	0.84	0.63 to 1.11	0.22
Odds ratio for eczema	0.98	0.94 to 1.02	0.26	1.00	0.92 to 1.08	0.92	1.02	0.94 to 1.11	0.60
Odds ratio for hay fever	0.97	0.91 to 1.02	0.23	0.98	0.88 to 1.09	0.76	1.03	0.93 to 1.16	0.56
FEV_1, ml	6	1 to 11	0.03 n = 202	21	9 to 33	0.001 n = 330	12	−1 to 25	0.07 n = 325
FVC, ml	6	0 to 11	0.04 n = 202	20	7 to 33	0.003 n = 331	10	−5 to 24	0.19 n = 325
FEF_{25-75}, ml/s	0.010	−0.001 to 0.021	0.08 n = 202	0.031	0.006 to 0.056	0.02 n = 330	0.018	−0.01 to 0.046	0.20 n = 323
ln DRR	−0.040	−0.001 to 0.080	0.05 n = 165	−0.020	−0.097 to 0.058	0.62 n = 274	−0.030	−0.108 to 0.047	0.44 n = 270
ln FE_{NO}	0	−0.01 to 0.02	0.54 n = 181	0.01	−0.03 to 0.05	0.51 n = 304	0	−0.03 to 0.03	0.94 n = 299
Odds ratio for atopy	0.98	0.93 to 1.03	0.44 n = 182	0.97	0.87 to 1.08	0.56 n = 305	1.04	0.93 to 1.16	0.54 n = 301

Definition of abbreviations: CI = confidence interval; BHR = bronchial hyperresponsiveness (PD20 < 7.8); DRR = dose–response ratio; FEF_{25-75} = forced expiratory flow, midexpiratory phase; FE_{NO} = exhaled nitric oxide.

Infants of low birth weight were excluded from the analysis. Logistic regression models for symptoms and atopy included the following as covariates: gestational age at scan, sex, maternal smoking status at first-trimester scan, smoke exposure at age 10 years, history of maternal asthma, Scottish Index of Multiple Deprivation, the infant's weight at birth, birth order, breast feeding, use of antibiotics by the child in the first year of life, visiting the doctor because of cough in the first 6 months, maternal intake of zinc and vitamins C and D, and maternal plasma tocopherol. Multiple linear regression models for spirometry, DRR, and FE_{NO} included the following variables: gestational age at scan, sex, maternal smoking status at first-trimester scan, smoke exposure at age 10 years, history of maternal asthma, maternal height, maternal first-trimester plasma alpha tocopherol, Scottish Index of Multiple Deprivation (36), birth weight, and child's height aged 10 years. The models for DRR and FE_{NO} also included atopy and FEV_1.

TABLE 3. REGRESSION COEFFICIENTS AND 95% CONFIDENCE INTERVALS FOR RESPIRATORY SYMPTOMS AND PHYSIOLOGIC MEASUREMENTS AT 10 YEARS OF AGE FOR INDIVIDUALS CATEGORIZED BY CHANGE IN CROWN–RUMP LENGTH (FIRST TRIMESTER) AND BIPARIETAL DIAMETER (SECOND TRIMESTER)

	Persistent Low Growth (*n = 99 unless stated*)			Growth Acceleration (*n = 65 unless stated*)			Growth Deceleration (*n = 47 unless stated*)			Persistent High Growth (*n = 122 unless stated*)
	Effect Size	95% CI	*P*	Effect Size	95% CI	*P*	Effect Size	95% CI	*P*	
Diagnosed asthma	2.80	1.17 to 6.91	0.02	2.44	0.92 to 6.46	0.07	1.07	0.31 to 3.67	0.91	1
Diagnosed asthma plus recent wheeze	4.93	1.46 to 16.6	0.01	5.15	1.38 to 19.2	0.02	1.11	0.18 to 6.80	0.91	1
Asthma medications	2.71	0.104 to 7.09	0.04	2.30	0.77 to 6.82	0.13	1.48	0.42 to 5.27	0.54	1
Wheeze ever	1.64	0.82 to 3.29	0.16	1.58	0.73 to 3.43	0.25	0.76	0.29 to 2.05	0.61	1
Wheeze last 12 mo	1.92	0.80 to 4.64	0.15	1.81	0.66 to 4.94	0.25	0.56	0.14 to 2.27	0.41	1
Eczema	0.92	0.46 to 1.86	0.83	2.52	1.21 to 5.26	0.01	0.73	0.29 to 1.87	0.52	1
Hay fever	0.64	0.27 to 1.53	0.31	0.85	0.35 to 2.11	0.85	0.10	0.01 to 0.82	0.03	1
FEV_1	−103	−194 to −13	0.03	−78	−178 to 22	0.12	−89	−192 to 14	0.09	0
			n = 48			n = 37			n = 32	n = 73
FVC	−107	−203 to −12	0.03	−49	−154 to 57	0.36	−116	−225 to −7	0.04	0
			n = 48			n = 37			n = 32	n = 37
FEF_{25-75}	−0.130	−0.427 to 0.065	0.19	−0.212	−0.427 to 0.003	0.05	−0.070	−0.292 to 0.151	0.53	0
			n = 48			n = 37			n = 32	n = 37
ln DRR	0.38	−0.23 to 0.99	0.22	−0.22	−0.90 to 0.46	0.53	−0.21	0.90 to 0.49	0.56	0
			n = 40			n = 29			n = 27	n = 58
ln FE_{NO}	−0.07	−0.24 to 0.22	0.95	0.09	−0.24 to 0.26	0.94	−0.11	−0.37 to 0.15	0.37	0
			n = 43			n = 32			n = 29	n = 69
Atopy	1.23	0.51 to 2.98	0.65	1.68	0.63 to 4.51	0.30	1.03	0.38 to 2.78	0.96	1
			n = 45			n = 31			n = 31	n = 65

Definition of abbreviations: CI = confidence interval; DRR = dose–response ratio; FEF_{25-75} = forced expiratory flow, midexpiratory phase; FE_{NO} = exhaled nitric oxide.

Infants of low birth weight were excluded from the analysis. Logistic regression models for symptoms and atopy included the following as covariates: gestational age at scan, sex, maternal smoking status at first-trimester scan, smoke exposure at age 10 years, history of maternal asthma, Scottish Index of Multiple Deprivation, the infant's weight at birth, birth order, breast feeding, visiting the doctor because of cough in the first 6 months, use of antibiotics by the child in the first year of life, maternal intake of zinc and vitamins C and D, and maternal plasma tocopherol. Multiple linear regression models for spirometry, DRR, and FE_{NO} included the following variables: gestational age at scan, sex, maternal smoking status at first trimester scan, smoke exposure at age 10 years, history of maternal asthma, maternal height, maternal first-trimester plasma alpha tocopherol, Scottish Index of Multiple Deprivation (36), birth weight, and child's height aged 10 years. The models for DRR and FE_{NO} also included atopy and FEV_1.

Longitudinal Analysis

There were 367 individuals where details of first-trimester size and respiratory symptoms were available at ages 5 and 10 years including 303 who wheezed at neither age; 20 who wheezed at both ages (persistent wheeze); 22 who wheezed at 5 but not 10 (transient wheeze); and 22 who wheezed at 10 but not 5 years of age (late-onset wheeze). Those with persistent wheeze were shorter in the first trimester by an average of 5.4 mm compared with those with wheeze at neither age (95% CI, −2.4 to −8.4; $P = 0.001$) (Figure 1). To put this reduction into context, the average first-trimester length was 44 mm. When categorized by quartile of CRL and compared with the longest quartile (n = 25), the mean % FEV_1 for the remaining groups was reduced at both 5 and 10 years ($P \leq 0.01$) (Figure 2). With reference to the longest group, % FEV_1 in the shortest group (n = 33) was reduced by an average of 9% (95% CI, 3–16; $P = 0.005$) at age 5 years and 8% (95% CI, 2–14; $P = 0.01$) at age 10 years; the second shortest group (n = 19) had a relative mean reduction of 14% (95% CI, 7–21; $P < 0.001$) at 5 years and 10% (95% CI, 4–17; $P = 0.003$) at 10 years; the second longest quartile (n = 30) had a mean reduction in % FEV_1 of 9% (95% CI, 3–15; $P = 0.005$) at age 5 years and 9% (95% CI, 4–16; $P = 0.002$) at age 10 years.

DISCUSSION

The main finding in the present study was that the shortest individuals in the first trimester were at increased risk for persistent wheeze, whereas the longest individuals had superior lung function at age 10 years. An additional finding was that changes in growth trajectory after the first trimester were associated with altered risk for eczema and hay fever. We also report that first-trimester size and size at birth are independently associated with lung function. These results demonstrate that the association between early fetal size and asthma outcomes persists beyond early childhood and is not subsumed by postnatal exposures. Spirometry and, to a lesser extent, asthma symptoms track from childhood into adulthood and, by extrapolation from other studies (21, 22) to ours, it is likely that early fetal size will continue to be related to postnatal respiratory outcomes beyond childhood. The previous results from our cohort (5, 9) and those of the Southampton Women's Survey Study Group

Figure 1. Comparison of mean crown rump length (bars indicating 95% confidence interval) across groups categorized by wheeze at ages 5 and 10 years. The analysis adjusted for gestation at scan, sex, maternal smoking, maternal asthma, maternal height, maternal plasma α-tocopherol at enrolment, birth weight, and Scottish Index of Multiple Deprivation.

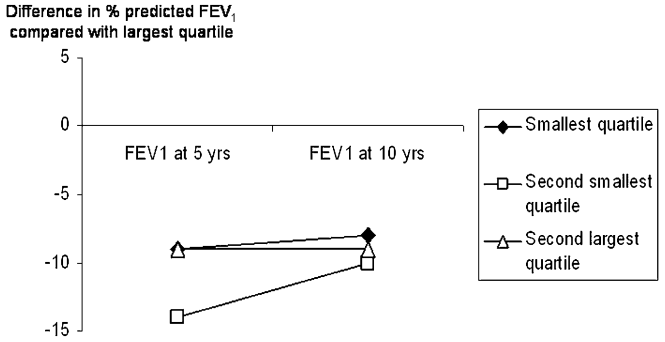

Figure 2. Mean percentage of predicted FEV_1 at ages 5 and 10 years in groups categorized by quartile of first-trimester fetal size. The reference group is the largest quartile and in comparison, the reductions in % FEV_1 were significant at both 5 and 10 years of age ($P \leq 0.01$).

(8) validate the use of fetal measurement as an index of antenatal respiratory status and point toward the origins of asthma being active in a very early stage of human development, and possibly shortly after conception, whereas the origins of eczema and hay fever may be determined after the first trimester. Interventions aimed at preventing asthma and reduced lung function are therefore more likely to be effective when implemented early in pregnancy.

In the only other cohort study that has related antenatal fetal measurements to respiratory outcomes, Pike and coworkers (8) describe an association between early (i.e., weeks 11–19) and late (i.e., weeks 19–34) growth acceleration and reduced wheeze that is not consistent with the present study (Tables 3 and E4). In the Southampton cohort, early growth acceleration was associated with increased risk for atopy and similar associations were seen in the present study for atopic conditions (i.e., eczema and hay fever) (Table 3). In our population, abdominal girth was not measured and third-trimester measurements were obtained at term and not 34-week gestation, so the results of the two studies may not be directly comparable. Despite differences between cohorts in terms of age at follow-up, fetal measurements made, and age at third-trimester measurement, the Southampton and Aberdeen cohorts provide evidence that fetal size and growth trajectories are important to respiratory outcomes in childhood. This consistency between populations is evidence that the associations are genuine and may be generalizable to other populations.

The results of the present report are also consistent with the findings we reported from the assessment of our study participants at age 5 years (Table 4) (9). For example, there are consistent associations between fetal size and asthma, but not wheeze. There are also consistent associations between fetal size and lung function, although those between BPD and lung function have become more marked at age 10 years than at 5 years and this might be caused by the increased range of lung function values at 10 years of age. There is one difference between the findings at ages 5 and 10 years: growth acceleration was associated with reduced lung function at age 5 years but growth deceleration was associated with reduced lung function at 10 years of age. The acceleration and deceleration groups were relatively small in size and so the clinical relevance of these apparent differences, which were not associated with altered risk for respiratory symptoms, is unclear. The overall internal consistency of results within our cohort when assessed at ages 5 and 10 years support the hypothesis that early fetal size is a determinant of life-long respiratory outcomes.

Given the transient nature of asthma symptoms in young children (10), the present analysis provides important insight into the durability of the relationship between fetal size and asthma outcomes. First-trimester fetal size was associated with current wheeze but not ever wheeze (Table 2), and wheeze that persisted at ages 5 and 10 years was associated with reduced first-trimester size (Figure 1). The phenomenon of remittent, persistent, and late-onset wheeze has been observed in many studies and different risk factors have been attributed to the different wheezing phenotypes; reduced fetal size in early pregnancy seems to be a risk factor for persistent wheeze, which is usually synonymous with asthma.

This is the first study to relate fetal size to bronchial hyperresponsiveness (BHR), a hallmark of asthma and airway remodeling, and we found no association (Tables 2 and 3). Additionally, there were no associations between fetal measurements and atopy or increased FE_{NO}, two additional physiologic outcomes that are associated with asthma. There is therefore an apparent inconsistency in our results because reduced early fetal size is associated with asthma symptoms and reduced lung function but not other physiologic characteristics of asthma. Atopy, BHR, and elevated FE_{NO} are all positively correlated (23) and are dependent on age at onset of atopy during childhood (24). Whereas the association between reduced lung function and asthma symptoms is established in early infancy (25, 26), the association between BHR and asthma symptoms is apparent at 12 months of age (27) with features of airway remodeling not evident until after infancy (28, 29). Therefore, the association we have observed between early fetal size and spirometry but not atopy, BHR, and FE_{NO} is consistent with the paradigm whereby

TABLE 4. SUMMARY OF OUTCOMES AT AGES 5 AND 10 YEARS IN THE CONTEXT OF FETAL SIZE AND CHANGING FETAL SIZE

	Risk of Asthma		Risk of Wheeze in Last Year		Mean Change in FEV_1 (*ml*)		Mean Change in FEF_{25-75} (*ml/s*)	
	5 yr	10 yr	5 yr	10 yr	5 yr	10 yr	5 yr	10 yr
Change per mm increase CRL	−4%	−6%	−3%	−6%	+4	+6	+0.006	+0.010
	$P = 0.04$	$P = 0.03$	$P = 0.18$	$P = 0.04$	$P = 0.009$	$P = 0.03$	$P = 0.07$	$P = 0.08$
Change per mm increase BPD	−12%	−9%	−3%	−7%	+4	+21	+0.003	+0.031
	$P = 0.008$	$P = 0.08$	$P = 0.46$	$P = 0.17$	$P > 0.05$	$P = 0.001$	$P = 0.47$	$P = 0.02$
Change per mm increase FL	−10%	−6%	−2%	−5%	+2	+12	+0.008	+0.018
	$P = 0.05$	$P = 0.31$	$P = 0.74$	$P = 0.34$	$P > 0.05$	$P = 0.07$	$P = 0.29$	$P = 0.20$
Persistent low CRL and BPD compared with persistent high growth	+300%	+280%	+238%	+192%	−27	−103	−0.035	−0.13
	$P = 0.008$	$P = 0.02$	$P = 0.01$	$P = 0.15$	$P = 0.25$	$P = 0.02$	$P = 0.51$	$P = 0.19$
Growth deceleration (CRL and BPD) compared with persistent high growth	+194%	+7%	−44%	−44%	−8	−89	0.003	−0.070
	$P = 0.19$	$P = 0.91$	$P = 0.20$	$P = 0.41$	$P = 0.83$	$P = 0.09$	$P = 0.98$	$P = 0.53$

Definition of abbreviations: BPD = biparietal diameter; CRL = crown–rump length; FEF_{25-75} = forced expiratory flow, midexpiratory phase; FL = femur length.

a primary airway risk factor for asthma is determined in early fetal life ("premodeling") leading to reduced airway diameter, whereas further risk factors, relating to atopy, airway inflammation, and remodeling, may also occur in utero (30), infancy, and childhood (31).

The present study was not designed to describe the mechanisms underlying the association between early fetal size and asthma outcomes but our previous work has given some insight into the potential relevance of maternal dietary factors (9) and maternal smoking (5). Our analysis adjusted for maternal smoking and dietary exposures and this suggests that other factors are also relevant. The Barker hypothesis (32) implicated maternal malnutrition during pregnancy in preprogramming postnatal morbidity but the mothers in our cohort were generally well nourished, although micronutrient deficiencies cannot be excluded (5). Associations between absolute fetal size and asthma outcomes were present when BPD was used as an index of second-trimester size but not FL (Table 2) and we speculate that this might indicate that factors influencing central somatic growth, but not peripheral somatic growth, are associated with pulmonary growth. Our observation that associations between size at birth and lung function persist when early fetal size is considered might suggest that the airway function is modified after the first trimester but before birth. The mechanism linking early fetal growth and asthma outcomes seems to be complex but may involve antenatal exposures determining the level of airway function, which is then modified by antenatal and postnatal factors, such as atopy, infections (33), and exposure to tobacco smoke (34).

There are a number of other factors that should be considered when interpreting these results. First, the fetal measurements were collected retrospectively and were not obtained for all individuals, in particular first-trimester measurements; this absence of data reduces the statistical power of the study and therefore weakens rather than strengthens the relationships reported. In particular, the apparent inconsistent association between early growth acceleration and asthma but not reduced FEV_1 might be explained by the small number of individuals where FEV_1 was measured. Second, as in many cohort studies, extended follow-up has resulted in drop-out and enrichment of other subjects who were larger in the second (but not first or third) trimester and who were more likely to have nonsmoking parents; although we have been able to describe these biases and consider these in our analysis, this remains a limitation to our study. Third, although we have been able to consider early life influences that may confound the relationship between fetal size and asthma outcomes, our study was not designed to measure environmental exposures between ages 5 and 10 years that may have influenced this relationship; any such confounders will act to weaken and not strengthen the relationships we describe. Fourth, multiple statistical tests have been undertaken and some of the significant results may have occurred by chance, although the consistency of our results with those from the earlier analysis of this cohort (9) and also with a similar cohort (8) makes it less likely that type II errors have occurred. Finally, unlike the Southampton study (8), we were not able to compare the same fetal measurement over time and assume that levels of growth in CRL and BPD in individuals are similar during these periods. The consistency of some of our findings with those of the Southampton group indicates that our comparison of first- and second-trimester fetal size is likely to be valid.

In summary, we have reported that longer first-trimester fetal size seems to protect against the development of early onset, persistent childhood asthma. In the developing human lung, airway development takes place during early fetal life but alveolar development is thought to begin in the latter stages of pregnancy and continue into postnatal life (35) and therefore exposures or relative deficiencies of nutrients after early infancy are also likely to influence respiratory outcomes.

Author Disclosure: None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

Acknowledgment: The authors are indebted to the parents and children who have taken part in the study since 1997. They are also grateful to the Medical Research Council and Tenovus Scotland for providing the funding that made the present study possible. The authors thank Dr. Shona Fielding for her statistical advice during resubmission of this manuscript.

References

1. Shaheen SO, Sterne JA, Montgomery SM, Azima H. Birth weight, body mass index and asthma in young adults. *Thorax* 1999;54:396–402.
2. Barker DJ, Godfrey KM, Fall C, Osmond C, Winter PD, Shaheen SO. Relation of birth weight and childhood respiratory infection to adult lung function and death from chronic obstructive airways disease. *Br Med J (Clin Res Ed)* 1991;303:671–675.
3. Canoy D, Pekkanen J, Elliott P, Pouta A, Laitinen J, Hartikainen AL, Zitting P, Patel S, Little MP, Järvelin MR. Early growth and adult respiratory function in men and women followed from the fetal period to adulthood. *Thorax* 2007;62:396–402.
4. Stein CE, Kumaran K, Fall CH, Shaheen SO, Osmond C, Barker DJ. Relation of fetal growth to adult lung function in south India. *Thorax* 1997;52:895–899.
5. Prabhu N, Smith N, Campbell D, Craig LC, Seaton A, Helms PJ, Devereux G, Turner SW. First trimester maternal tobacco smoking habits and fetal growth. *Thorax* 2010;65:235–240.
6. Devereux G. The increase in the prevalence of asthma and allergy: food for thought. *Nat Rev Immunol* 2006;6:869–874.
7. Rusconi F, Galassi C, Forastiere F, Bellasio M, De Sario M, Ciccone G, Brunetti L, Chellini E, Corbo G, La Grutta S, *et al*. Maternal complications and procedures in pregnancy and at birth and wheezing phenotypes in children. *Am J Respir Crit Care Med* 2007;175:16–21.
8. Pike KC, Crozier SR, Lucas JS, Inskip HM, Robinson S, Roberts G, Godfrey KM, The Southampton Women's Survey Study Group. Patterns of fetal and infant growth are related to atopy and wheezing disorders at age 3 years. *Thorax* 2010;65:1099–1106.
9. Turner SW, Campbell D, Smith N, Craig LC, McNeill G, Forbes SH, Harbour PJ, Seaton A, Helms PJ, Devereux GS. Associations between fetal size, maternal alpha-tocopherol and childhood asthma. *Thorax* 2010;55:555–561.
10. Henderson J, Granell R, Heron J, Sherriff A, Simpson A, Woodcock A, Strachan DP, Shaheen SO, Sterne JA. Associations of wheezing phenotypes in the first 6 years of life with atopy, lung function and airway responsiveness in mid-childhood. *Thorax* 2008;63:974–980.
11. Anonymous. Worldwide variations in the prevalence of asthma symptoms: the International Study of Asthma and Allergies in Childhood (ISAAC). *Eur Respir J* 1998;12:315–335.
12. Martindale S, McNeill G, Devereux G, Campbell D, Russell G, Seaton A. Antioxidant intake in pregnancy in relation to wheeze and eczema in the first two years of life. *Am J Respir Crit Care Med* 2005;171:121–128.
13. Robinson HP, Fleming JE. A critical evaluation of sonar "crown-rump length" measurements. *Br J Obstet Gynaecol* 1975;82:702–710.
14. Chitty LS, Altman DG, Henderson A, Campbell S. Charts of fetal size: 4. Femur length. *Br J Obstet Gynaecol* 1994;101:132–135.
15. Chitty LS, Altman DG, Henderson A, Campbell S. Charts of fetal size: 2. Head measurements. *Br J Obstet Gynaecol* 1994;101:35–43.
16. Freeman JV, Cole TJ, Chinn S, Jones PRM, White EM, Preece MA. Cross sectional stature and weight reference curves for the UK, 1990. *Arch Dis Child* 1995;73:17–24.
17. De Biasio P, Prefumo F, Lantieri PB, Venturini PL. Reference values for fetal limb biometry at 10–14 weeks of gestation. *Ultrasound Obstet Gynecol* 2002;19:588–591.
18. American Thoracic Society. Recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide. *Am J Respir Crit Care Med* 2005;171:912–930.

19. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CP, Gustafsson P, *et al*. Standardisation of spirometry. *Eur Respir J* 2005;26:319–338.
20. Hoo AF, Stocks J, Lum S, Wade AM, Castle RA, Costeloe KL, Dezateux C. 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.
21. Stern DA, Morgan WJ, Wright AL, Guerra S, Martinez FD. Poor airway function in early infancy and lung function by age 22 years: a non-selective longitudinal cohort study. *Lancet* 2007;370:758–764.
22. Phelan PD, Robertson CF, Olinsky A. The Melbourne Asthma Study: 1964–1999. *J Allergy Clin Immunol* 2002;109:189–194.
23. Franklin PJ, Turner SW, Le Souef PN, Stick SM. Exhaled nitric oxide and asthma: complex interactions between atopy, airway responsiveness, and symptoms in a community population of children. *Thorax* 2003;58: 1048–1052.
24. Turner SW, Heaton T, Rowe J, Suriyaarachchi D, Serralha M, Holt BJ, Franklin PJ, Stick SM, Goldblatt J, Sly PD, *et al*. Early-onset atopy is associated with enhanced lymphocyte cytokine responses in 11-year-old children. *Clin Exp Allergy* 2007;37:371–380.
25. Håland G, Carlsen KC, Sandvik L, Devulapalli CS, Munthe-Kaas MC, Pettersen M, Carlsen KH, for ORAACLE. Reduced lung function at birth and the risk of asthma at 10 years of age. *N Engl J Med* 2006;355:1682–1689.
26. Turner SW, Palmer LJ, Rye PJ, Gibson NA, Judge PK, Cox M, Young S, Goldblatt J, Landau LI, Le Souëf PN. The relationship between infant airway function, childhood airway responsiveness and asthma. *Am J Respir Crit Care Med* 2004;169:921–927.
27. Turner SW, Young S, Goldblatt J, Landau LI, Le Souef PN. Childhood asthma and increased airway responsiveness: a relationship that begins in infancy. *Am J Respir Crit Care Med* 2009;179:98–104.
28. Saglani S, Malmström K, Pelkonen AS, Malmberg LP, Lindahl H, Kajosaari M, Turpeinen M, Rogers AV, Payne DN, Bush A, *et al*. Airway remodeling and inflammation in symptomatic infants with reversible airflow obstruction. *Am J Respir Crit Care Med* 2005;171: 722–727.
29. Saglani S, Payne DN, Zhu J, Wang Z, Nicholson AG, Bush A, Jeffery PK. Early detection of airway wall remodeling and eosinophilic inflammation in preschool wheezers. *Am J Respir Crit Care Med* 2007; 176:858–864.
30. Devereux G, Barker RN, Seaton A. Antenatal determinants of neonatal immune responses to allergens. *Clin Exp Allergy* 2002;32:43–50.
31. Turner SW, Palmer LJ, Rye PJ, Gibson NA, Young S, Goldblatt J, Landau LI, Le Souëf PN. Determinants of airway responsiveness to histamine in children. *Eur Respir J* 2005;25:462–467.
32. Barker DJ. The Wellcome Foundation Lecture, 1994. The fetal origins of adult disease. *Proc R Soc Lond B Biol Sci* 1995;262:37–43.
33. Kusel MM, de Klerk NH, Kebadze T, Vohma V, Holt PG, Johnston SL, Sly PD. Early-life respiratory viral infections, atopic sensitization, and risk of subsequent development of persistent asthma. *J Allergy Clin Immunol* 2007;119:1105–1110.
34. Strachan DP, Cook DG. Health effects of passive smoking. 6. Parental smoking and childhood asthma: longitudinal and case-control studies. *Thorax* 1998;53:204–212.
35. 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.
36. SIMD. Office of the Chief Statistician, Scottish Executive. Scottish Index of Multiple Deprivation 2006: technical report [accessed Sept 8, 2010]. Available from: http://www.scotland.gov.uk/Publications/2006/10/13142913/0.