First trimester fetal size and prescribed asthma medication at 15 years of age

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ABSTRACT There is increasing evidence that antenatal factors predispose to childhood asthma. We tested the hypothesis that reduced first trimester fetal size is associated with increased risk for asthma at 15 years of age.

Fetal size in the first and second trimester was ascertained by ultrasound scan. The primary outcome of being dispensed one or more asthma medications by the family doctor in the year before the 15th birthday was determined from routinely acquired dispensing data.

Dispensing data were available for 1699 (88% of the original cohort) participants at 15 years of age and questionnaire data for 750 (39%). Each reduction in z-score for first trimester size was associated with increased odds for dispensed asthma medication at 15 years of age (OR 1.26, 95% CI 1.03–1.54) and self-reported use of asthma medications (OR 1.55, 95% CI 1.16–2.08). Overall, first and second trimester size and forced expiratory volume in 1 s at ages 5, 10 and 15 years were reduced for those dispensed asthma medications compared with those not dispensed asthma medications (p=0.003).

Antenatal factors that are active by the first trimester may contribute to respiratory well-being throughout childhood. Dropout from a birth cohort study can overestimate of the magnitude of any true association.

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Introduction

Asthma and chronic obstructive pulmonary disease (COPD) are common respiratory conditions that are characterised by airflow obstruction. Childhood asthma symptoms usually develop in the pre-school years and cohort studies have demonstrated that abnormalities in lung function are present from early infancy, before the onset of symptoms [1–4]. Reduced lung function in infancy is also known to persist into early adulthood [2, 5]. Although COPD is an adult condition, the early origins of COPD are apparent in childhood as reduced birthweight is a risk factor for COPD and reduced lung function in adult life [6, 7], while recent work has identified how obstructed lung function and asthma in childhood precede COPD in the sixth and seventh decades of life [8–10]. Collectively, these results indicate that the abnormalities in pulmonary physiology associated with asthma and COPD are apparent at birth, but what remains uncertain is when these abnormalities are first apparent *in utero*.

Fetal anthropometric measurements, ascertained by antenatal ultrasound scan, have been used as an index of *in utero* lung function and related to postnatal respiratory outcomes [11–15], and the rationale for this is collinearity between anthropometric measurements such as sitting height and ulna length and childhood lung function [16, 17]. Reduced antenatal fetal measurements are associated with reduced lung function at 5, 6 and 10 years of age [12–15]. The relationship between fetal measurements and asthma symptoms is less consistent, with two cohorts observing associations between reduced fetal size or change in fetal size and increased risk for asthma symptoms [11, 13, 15], but this was not replicated in a third cohort [12, 14]. The apparently inconsistent findings between cohorts for associations between fetal size and symptoms may reflect differences in response bias and differences in methodologies, including definitions used and age at assessment. However, there is also a recognised disconnect between reduced lung function and asthma symptoms, and thus a relationship may not be apparent in every population [18].

Lung function and the prevalence of asthma symptoms continue to change during the transition from childhood to adulthood, *e.g.* asthma prevalence rises in females but falls in males during puberty, and it is therefore important to replicate in adolescents any associations seen in childhood [19, 20]. Conventional follow-up of birth cohorts requires making contact with the participants. However, dropout of participants and ensuing biases, particularly during adolescence, are major limitations to birth cohort studies; a solution to this is the use of routinely acquired healthcare data [21, 22]. Here, we test the hypothesis that reduced fetal size is associated with increased risk for asthma. Our primary outcome was being dispensed one or more asthma medications at 15 years of age and was determined through linkage to primary care dispensing data. A secondary outcome was self-reported receipt of asthma medication. We also undertook a longitudinal analysis of fetal size (an index of fetal lung size) and childhood spirometry in those dispensed compared with those not dispensed one or more asthma medications at 15 years of age.

Materials and methods

Study design

A birth cohort was recruited to answer the question "What is the relationship between early dietary encounters and childhood asthma?" [23]. The cohort was recruited in Aberdeen, the main city in the north-east of Scotland, UK. Figure 1 summarises the data collected at the different time-points in the cohort's follow-up. Mothers attending a routine first trimester ultrasound scan to date the pregnancy were recruited between 1997 and 1999 (median gestation 10 weeks). The supplementary material presents details of the characteristics of participants relative to the general population and questions asked at recruitment. Routinely collected ultrasound scan measurements were obtained retrospectively in 2008 from the paper records made at the time of imaging. We sought to follow-up the whole cohort at 15 years of age by replicating the methodology of previous assessments at 5 and 10 years of age. Participants were asked to complete and return a postal respiratory questionnaire, and also attend a clinical assessment where height, weight and spirometry were measured and allergen skin prick reactivity determined. The supplementary material describes the questionnaire in more detail. The Prescribing Information System (PIS) data held by NHS Scotland was used to identify whether those study participants still living in Scotland had been dispensed one or more asthma medications in the 12 months prior to their 15th birthday using the same methodology described previously [22]. The PIS system was introduced in 2009 and by 2014 more than 98% of general practitioner prescriptions were included for the whole population [24]. In the UK, asthma medications are only available by prescription, but some eczema treatments such as emollients and weak topical corticosteroids (*i.e.* hydrocortisone) may be bought without prescription. The PIS system is therefore able to identify individuals who have been prescribed asthma medications, but also those who have not been prescribed medications, and still living in Scotland. At each of the three childhood assessments, separate medical ethics committee approval was obtained, and written parental consent and verbal assent from the child were also obtained. Separate ethical approval and approval from the Public Benefit and Privacy Panel for Health and Social Care committee were obtained for the linkage with the PIS database.

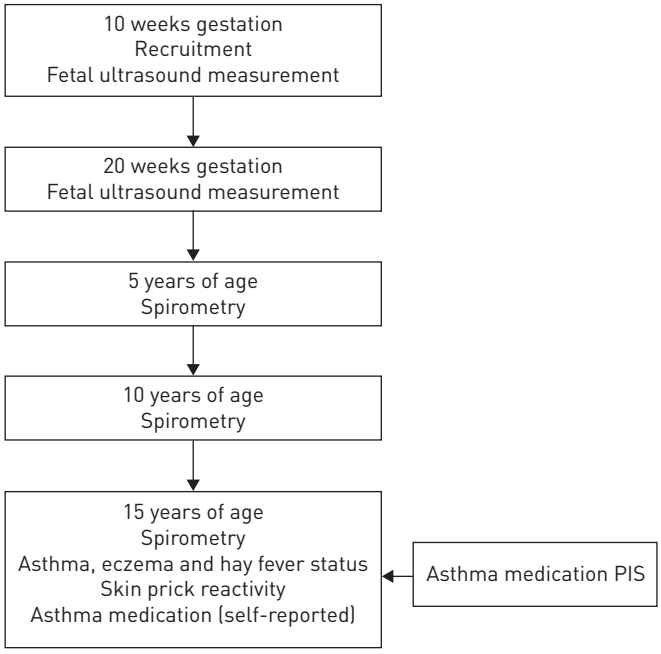

FIGURE 1 Flow diagram showing the age at which data analysed in the present study were collected. PIS: Prescribing Information System.

Fetal measurements

Fetal measurements were obtained from paper records held in the mother's hospital notes. The crown–rump length (CRL) was measured in the first trimester (*i.e.* ⩽13 weeks gestation). Biparietal diameter (BPD) and femur length were measured in the second trimester (*i.e.* 14–28 weeks gestation). Fetal measurements were adjusted for gestation [25], and expressed as a z-score to allow comparison between CRL, BPD, femur length and spirometry. See supplementary material for the definition of gestation and details of reproducibility of ultrasound measurements.

Clinical assessment in childhood

The same standard methodology for spirometry and skin prick testing used at 10 years of age was used at 15 years of age (see supplementary material for full details)

Analysis

Characteristics of participants were described using numbers and percentages for categorical variables and means and standard deviations for continuous outcomes (z-scores). Associations between fetal size and outcomes at 15 years of age were described using linear regression for continuous outcomes (*e.g.* lung function) and logistic regression for dichotomous outcomes (*e.g.* asthma yes/no). The supplementary material describes covariates used. As described previously [13, 15], the first (*i.e.* CRL) and second trimester (*i.e.* femur length) fetal z-scores were dichotomised about the median value to create groups of "larger" and "smaller" fetuses, and then PIS outcomes were compared across groups stratified by first and second trimester size (*i.e.* larger/larger, larger/smaller, smaller/larger and smaller/smaller). A linear mixed effects model assessed whether the trajectory of fetal measurements and forced expiratory volume in 1 s (FEV_1) z-scores were different for those with and without PIS-confirmed prescription for asthma medications at 15 years of age. Fixed effects of time, asthma group maternal asthma, maternal smoking during pregnancy (which we have demonstrated is associated with second but not first trimester fetal size [26]) and an index of deprivation (the Scottish Index of Multiple Deprivation (SIMD) [27]) were included using unstructured covariance for the repeated time. An interaction term of time with group was fitted to ascertain if the trajectory was different for the two groups. Models were adjusted for maternal asthma, maternal smoking (known to affect fetal size [28]) and SIMD. Sex was not used as an adjustment variable as it was used in the calculation of the z-score. Standard statistical software was used: SPSS version 24.0.0 (IBM, Armonk, NY, USA) and SAS version 9.3 (SAS Institute, Cary, NC, USA).

Results

Study participants

There were 1924 live-born singleton infants and PIS provided asthma dispensing data for 1699 of these (88%), of whom 170 (10%) were dispensed asthma medications at 15 years of age and 133 (8%) were

prescribed eczema medications. Questionnaires were returned for 750 (39%) participants at 15 years of age, of whom 96 reported being prescribed asthma medications; medication categories were provided by 70 of these individuals, of whom 37 were prescribed short-acting β-agonists, 23 were prescribed inhaled corticosteroids plus short-acting β-agonists and 10 were prescribed inhaled corticosteroids plus long-acting β-agonists and/or leukotriene receptor antagonists. The FEV_1 z-score was available in 514 (26%) study participants. Table 1 presents details of those assessed at 15 years of age for the whole cohort and for those where dispensing data were available. Individuals with PIS data available were representative of the original cohort in terms of socioeconomic status and maternal smoking, but those where questionnaires were returned were more likely to come from affluent communities and less likely to have mothers who smoked during pregnancy (table 1). For the 698 participants with asthma dispensing data available from both questionnaire and PIS data, there were 670 (96%) concordant results (72 dispensed and 598 not dispensed asthma medications); there were 19 individuals at 15 years of age who reported being prescribed medications where the PIS record indicated no prescription had been dispensed (false positive) and nine individuals with no self-report of being prescribed medication but who had a record on PIS of a prescription having being dispensed (false negative). The positive and negative predictive values for self-reported treatment against dispensing records were 97% and 89%, respectively.

TABLE 1 Details of the whole cohort, participants where data were available from the Prescribing Information System (PIS) and participants where data were available from questionnaires and clinical assessments at 15 years of age

	Original population	PIS data available at 15 years of age	Questionnaire returned at 15 years of age
Participants	1924[#]	1699[#]	750[#]
Male	50 (968)	50 (854)	46 (340)
Deprivation quintile[¶]			
SIMD 1	15 (284)	16 (266)	10 (72)
SIMD 2	9 (167)	9 (157)	8 (55)
SIMD 3	14 (268)	14 (238)	15 (105)
SIMD 4	22 (420)	23 (380)	23 (165)
SIMD 5	39 (734)	38 (647)	44 (317)
Maternal smoking during pregnancy	29 (566)	30 (518/1698)	19 (135/719)
Maternal asthma	16 (316)	17 (288/1698)	15 (110/719)
CRL z-score	0±1.00 (n=1206)	0.005±0.99 (n=1170)	0.034±0.93 (n=476)
BPD z-score	0±1.00 (n=1676)	0.002±0.99 (n=1622)	0.020±0.98 (n=623)
Femur length z-score	0.00±1.00 (n=1670)	0.010±1.00 (n=1616)	0.040±1.02 (n=622)
Birthweight kg	3.41±0.61 (n=1841)	3.44±0.56 (n=1815)	3.48±0.56 (n=691)
Wheeze in the last 12 months	NA	NA	15 (115/750)
Asthma diagnosed by physician	NA	NA	20 (147/750)
Asthma medications	NA	NA	13 (96/748)
Current eczema	NA	NA	16 (121/750)
Current hay fever	NA	NA	36 (270/750)
Skin prick positive[+]	NA	NA	44 (244/549)
Currently exposed to cigarette smoke	NA	NA	5 (34/686)
FEV_1 z-score	NA	NA	−0.18±1.05 (n=514)
$FEF_{25–75}$ z-score	NA	NA	0.12±0.96 (n=515)

Data are presented as n, % (n) or mean±SD. SIMD: Scottish Index of Multiple Deprivation; CRL: crown–rump length; BPD: biparietal diameter; FEV_1: forced expiratory volume in 1 s; $FEF_{25–75}$: forced expiratory flow at 25–75% of forced vital capacity; NA: not assessed. [#]: unless otherwise indicated; [¶]: 1=most deprived quintile, 5=least deprived quintile [27]; [+]: defined as a wheal ⩾3 mm to house dust mite, cat, timothy grass and egg.

Relationship between fetal size and asthma dispensing data at 15 years of age

The mean±SD first trimester z-score was −0.186±1.06 (n=111) for 15 year olds dispensed any asthma medication and 0.024±0.99 (n=954) for those not dispensed asthma medication. The odds ratio for being dispensed asthma medications at 15 years of age was increased by 1.26 (95% CI 1.03–1.54) for each z-score reduction in first trimester fetal size (p=0.027) (table 2). There was no difference in second trimester fetal size between those dispensed asthma medication or not at 15 years of age (table 2). There was no relationship between any fetal measurements and being dispensed eczema medications at 15 years of age (table 2). There was no difference in the proportion of 15 year olds who were dispensed asthma medications across the groups stratified by first and second trimester fetal size (supplementary table S1).

Relationship between fetal size and self-reported symptoms and spirometry at 15 years of age

Reduced CRL and femur length were associated with increased risk for self-reported doctor-diagnosed asthma, recent wheeze and receipt of asthma medications (table 3). There were no associations between fetal measurements and current eczema, current hay fever or skin prick positivity (table 3). Supplementary table S2 shows that the proportion with asthma was lower in the large/large group, but was not statistically significantly different from the other three groups. Fetal measurements were not associated with lung function (FEV_1 or forced expiratory flow at 25–75% of forced vital capacity) at 15 years of age (table 3).

Trajectory of z-scores from 10 weeks gestation to 15 years of age for those with and without dispensed asthma medications at 15 years of age

The linear mixed effects model, which combined fetal measurements and FEV_1 during childhood and related these to PIS data, found that overall there was a reduction in z-score measurements of 0.20 (95% CI −0.33–−0.06) between those who were and were not dispensed asthma medications at 15 years of age. When second trimester size was removed from the analysis, the mean reduction in CRL/FEV_1 z-score was −0.23 (95% CI −0.38–−0.07). Figure 2 demonstrates that the reduction in the z-score for lung function (CRL and femur length as a proxy) was significantly different between the two groups between 10 weeks gestation and 15 years of age, although not significant at each individual assessment. There were no differences in z-scores for height during childhood between those with and without asthma, indicating that the association with reduced CRL and FEV_1 and asthma is not explained by small fetuses with small lungs.

Discussion

This study described the relationship between reduced fetal size and asthma outcomes at 15 years of age, and the main finding was that reduced fetal size at 10 weeks gestation was associated with increased risk for requiring asthma medications in 15 year olds. A second finding was that those who were prescribed

TABLE 2 Relationship between first and second trimester fetal size and dispensed asthma and eczema medications at 15 years of age

	First trimester CRL z-score	Second trimester BPD z-score	Second trimester femur length z-score
Asthma			
Asthma prescriptions	−0.186±1.06 (n=111)	−0.002±1.00 (n=146)	−0.081±1.03 (n=145)
No asthma prescriptions	0.024±0.99 (n=954)	−0.008±0.98 (n=1320)	0.013±0.97 (n=1315)
OR[#] (95% CI) for asthma (for 1 SD decrease in z-score)	1.26 (1.03–1.54)[¶]	0.99 (0.83–1.19)	1.10 (0.92–1.32)
Eczema			
Eczema prescriptions	0.011±0.92 (n=85)	0.054±1.03 (n=111)	0.044±1.17 (n=111)
No eczema prescriptions	0.002±1.00 (n=980)	−0.013±0.98 (n=1355)	0.0008±0.96 (n=1349)
OR[#] (95% CI) for eczema (for 1 SD decrease in z-score)	1.01 (0.81–1.27)	0.93 (0.76–1.14)	0.96 (0.78–1.17)

Data are presented as mean±SD, unless otherwise stated. Gestation and sex were included in the calculation of z-scores, but not included in the logistic model. CRL: crown–rump length; BPD: biparietal diameter. [#]: logistic regression adjusted for maternal smoking during pregnancy and maternal history of asthma; [¶]: p=0.027.

TABLE 3 Relationship between first and second trimester fetal size and self-reported symptom or respiratory outcome at 15 years of age per z-score decrease in fetal measurement

	First trimester CRL	Second trimester BPD	Second trimester femur length
Asthma[#]	1.43 (1.12–1.84)[+]	1.19 (0.96–1.47)	1.35 (1.10–1.65)[+]
Recent wheeze[#]	1.31 (1.06–1.61)[§]	1.03 (0.86–1.23)	1.20 (1.01–1.42)[§]
Receipt of asthma medications[#]	1.55 (1.16–2.08)[+]	1.20 (0.92–1.56)	1.30 (1.03–1.66)[§]
Current eczema[#]	1.07 (0.82–1.42)	1.07 (0.85–1.35)	0.97 (0.78–1.20)
Current hay fever[#]	1.22 (0.99–1.50)	1.02 (0.87–1.23)	1.08 (0.91–1.27)
Atopy[#]	1.08 (0.85–1.38)	0.99 (0.80–1.22)	1.00 (0.82–1.21)
FEV_1 z-score[¶]	0.003 (−0.12–0.13)	0.039 (−0.07–0.15)	0.0 (−0.10–0.10)
FEF_{25-75} z-score[¶]	−0.035 (−0.15–0.08)	0.028 (−0.07–0.12)	0.020 (−0.07–0.11)

CRL: crown–rump length; BPD: biparietal diameter; FEV_1: forced expiratory volume in 1 s; FEF_{25-75}: forced expiratory flow at 25–75% of forced vital capacity. [#]: odds ratio for outcome (95% CI) per z-score decrease in fetal measurement (logistic regression adjusted for maternal smoking during pregnancy, maternal history of asthma and sex); [¶]: coefficient (95% CI) per z-score reduction (linear regression adjusted for maternal smoking during pregnancy, maternal history of asthma (sex, age and height were included in the calculation of z-scores and not included as covariates)); [+]: p<0.01; [§]: p<0.05.

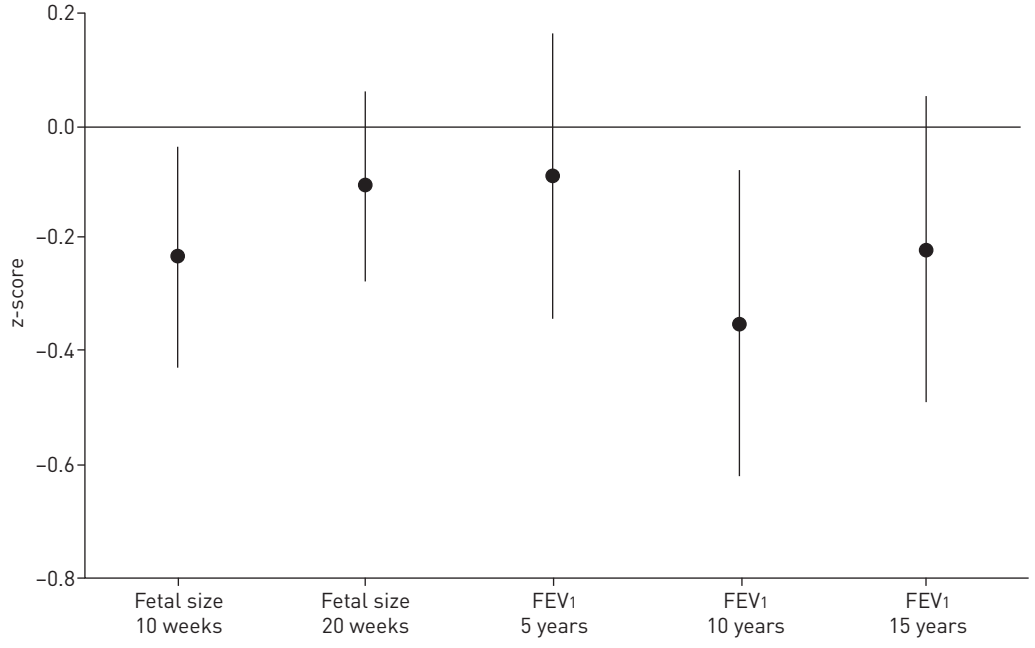

FIGURE 2 Comparison of mean z-scores (95% CI) of fetal measurements at 10 and 20 weeks gestation and mean z-scores (95% CI) of forced expiratory volume in 1 s (FEV_1) at 5, 10 and 15 years in children dispensed asthma medications at 15 years of age with reference to children not dispensed asthma medications at 15 years of age. The longitudinal analysis (a linear mixed effects model) considered z-scores of fetal measurements and FEV_1, and demonstrated an overall reduction in fetal size/FEV_1 z-score of 0.20 (95% CI −0.33– −0.06; p=0.003) between those dispensed asthma medications compared with the reference group.

asthma medications in the year prior to their 15th birthday had an overall reduction in fetal size and FEV_1 between 10 weeks gestation and 15 years of age (most notable at 10 weeks gestation and 10 years of age). There was no association between fetal size and atopic outcomes, including skin prick reactivity, hay fever and eczema. These observations suggests that mechanisms active in early pregnancy are associated with increased risk for asthma and that the mechanisms involve reduced lung function (lung development), but are independent of atopy (immunological development).

A major strength of this work is that we used linkage with routinely acquired dispensing data to enable follow-up for 88% of our cohort to 15 years of age; consequently the associations with asthma dispensing

should be minimally affected by bias due to nonparticipation. A second strength is that by applying a recently described methodology [25] to derive standardised fetal measurements, we have increased the power of our study by including fetal measurements from a greater number of individuals than the previous reports from our cohort [13, 15]. Due to the nonlinear relationship between fetal size and gestation we had previously restricted data to fetal measurements made between 8–12 and 18–22 weeks gestation and applying a linear method to derive standardised measurements. Some cases of asthma may be unrecognised by parents and undiagnosed by physicians, and a further strength of our study was that the questionnaire data allowed us to consider the relationship between participant-reported wheeze and fetal size, and we saw similar associations between wheeze and asthma (table 3) that suggest that our results were not significantly affected by individuals with undiagnosed asthma. A further strength to the present report is that our previous work describing associations between first trimester size and asthma outcomes at 5 and 10 years of age was limited to 501 and 350 study participants [13, 15], respectively, and here we extend this association to 15 years of age in 1170 study participants.

To the best of our knowledge, this is the first study to directly compare self-reported and objectively recorded need for asthma treatment in young people. The findings demonstrate that results from cohort studies reliant on active participation for follow-up are biased away from the null and not generalisable when there is the substantial dropout such as we experienced; the 61% dropout we experienced at 15 years of age is not unusual for a birth cohort. The association between first trimester size and self-reported outcomes was consistent with that between first trimester size and dispensing data, but had a relatively larger magnitude (OR 1.55 *versus* 1.26). There was an apparent false-positive result between self-reported asthma medication and second trimester femur length that was not confirmed when femur length was related to routinely acquired dispensing data. The difference in association between fetal size by self-reported and objectively recorded asthma treatment use is likely to be partly due to bias in follow-up, but also to less than perfect self-reporting of asthma medication use (negative predictive value 89%).

In adult cohorts, there is evidence that dropout may not substantially bias outcomes [29, 30]; however, in birth cohort studies, dropout does introduce considerable bias [21, 31]. One explanation for this may be that parents and not the participants give consent to join birth cohort studies, and when given the opportunity in later follow-up assessments, participants decline to take part. Our study also suggests the choice of fetal measurement considered in the analysis may also be important. While first trimester CRL appears to be a viable surrogate for lung development *in utero*, second trimester BPD appears to be a poor surrogate for lung development and including these measurements in the longitudinal modelling introduced a null bias.

These findings are consistent with our previous work that described associations between fetal size and asthma outcomes at 5 and 10 years of age [13, 15]. In the only other cohort to have linked fetal size to lung function, Sonnenschein *et al.* [14] reported an association between reduced fetal weight and reduced lung function from the second trimester, but found no association between antenatal growth and childhood asthma. There are a number of differences between our study and that of Sonnenschein *et al.* [14], and these include the definition of asthma used, the fetal measurements made, the ethnic mix within our populations and differences in follow-up rates, and these might explain apparent differences in outcomes for asthma symptoms. The results presented here should be treated with caution until replicated in other populations.

Asthma is a condition that affects the airways and these are developed in the 16-week-old fetus [32], so it is highly plausible that the level of lung function (as evidenced by fetal length) in the first trimester may track through the life course, at least to 15 years of age. Clearly, the level of lung function is modified in the postnatal period, and factors such as sex and maternal smoking have different associations with lung function at different stages in the life course [33]; this may explain why we saw no association between fetal size and spirometry at 15 years of age.

In the longitudinal analysis of fetal size and childhood FEV_1 there were reductions in first trimester size and lung function at 10 years of age for those prescribed asthma medications compared with others, but there was no reduction in second trimester size nor spirometry at 5 or 15 years of age. This apparently inconsistent result may be explained by a relative increase in variability of second trimester fetal measurements and spirometry in young children and/or different factors determine lung size compared with femur and head size. First trimester fetal size is known to be a good predictor of birthweight [34], has also been linked to cardiovascular outcomes in children [35] and in our previous work has been more consistently related to respiratory outcomes compared with second trimester fetal measurements [13, 15].

There are some limitations to this study that should be considered when interpreting the results. First, we cannot be certain that some individuals who reported use of asthma medication that was not confirmed on the PIS record were not using inhalers intended for other family members; the PIS data capture

prescribing in Scotland and so it is unlikely that the participants had obtained medication from other countries. Second, as with all routinely acquired data sources, the PIS database is not 100% complete and the apparent "false positive" reported in asthma medication receipt in 19 individuals may at least partly be explained by this incompleteness. This "missingness" will be at random and not bias the sample, but will wrongly categorise some individuals who have been prescribed asthma medication as not having been prescribed them and thus weaken the associations we describe. Third, while we know that asthma medications can only be obtained by prescription in Scotland, some medications for the most mild eczema symptoms may be obtained without prescription and therefore the absence of associations with eczema prescription should be interpreted with some caution. Fourth, fetal growth is partly driven by antenatal cues and the environment that our study participants was exposed to may be different to those in other populations; thus, our findings therefore require replication elsewhere. Finally, fetal measurements were retrospectively collected from routine antenatal surveillance scans and this may have introduced greater interoperator variability for fetal measurements compared with a prospective research study and measurements were missing in a number of individuals. However, increasing variability and missing data are likely to weaken and not strengthen the associations we describe.

In summary, this study has been able to link first trimester fetal measurements to respiratory outcomes at a later age and with greater case ascertainment than any other cohort, and the findings indicate that factors that determine early fetal development may be important determinants of respiratory well-being throughout childhood. Further follow-up of this cohort is planned and this could add to our understanding of the early origins of obstructive airways disease.

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