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

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Take home message: Reduced first trimester size is associated with increased risk for asthma throughout childhood.

ABSTRACT

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

Methods. Fetal size in the first (T1) and second (T2) trimesters were ascertained by ultrasound scan. The primary outcome of being dispensed ≥1 asthma medication by the family doctor in the year before the 15th birthday was determined from routinely acquired dispensing data.

Results. Dispensing data were available in 1699 fifteen year olds (88% of the original cohort) and questionnaire data in 750 (39%). Each reduction in z score for T1 size was associated with increased odds for dispensed asthma medication at 15 years (OR = 1.26, 95 %CI (1.02, 1.54)) and self-reported use of asthma medications (OR=1.55, 95% CI (1.16, 2.08). Overall, there was reduced T1 and T2 size and reduced FEV_1 at ages 5, 10 and 15 for those dispensed asthma medications compared to those not dispensed asthma medications (p=0.003).

Conclusion. Antenatal factors which are active by T1 may contribute to respiratory wellbeing throughout childhood. Drop out from a birth cohort study can overestimate of the magnitude of any true association.

Key words: Asthma, Epidemiology, Child, Fetus, Longitudinal Studies

INTRODUCTION

Asthma and Chronic Obstructive Pulmonary Disease (COPD) are common respiratory conditions which are characterised by airflow obstruction. Childhood asthma symptoms usually develop in the preschool 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 since reduced birth weight is risk factor for COPD[6] and reduced lung function in adult life[7], whilst 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 post-natal 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 five[12,13], six[14] and ten years of age[15]. The relationship between fetal measurements and asthma symptoms is less consistent, with two cohorts observing associations between reduced fetal size[13,15] or change in fetal size[11,13,15] and increased risk for asthma symptoms but this was not replicated in a third[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; but also there is a recognised disconnect between reduced lung function and asthma symptoms[18] and thus a relationship may not be apparent in every population.

Lung function and the prevalence of asthma symptoms continue to change during the transition from childhood to adulthood[19,20], for example asthma prevalence rises in females but falls in males during puberty[20], and it is therefore important to replicate in adolescents any associations seen in childhood. Conventional follow up of birth cohorts requires making contact with the participants, however drop out of participants and ensuing biases[21], particularly during adolescence, are major limitations to birth cohort studies; a solution to this is the use of routinely acquired health care data[22]. Here we test the hypothesis that reduced fetal size is associated with increased risk for asthma. Our primary outcome was being dispensed ≥1 asthma medication 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 to those not dispensed ≥1 asthma medication 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. Figure one 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 online data supplement 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 previous assessments at five and ten years. 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 on line data supplement 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 ≥1 asthma medication in the 12 months prior to the fifteenth birthday using the same methodology previously described [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. On each of the three childhood assessments, separate medical ethics committee approval was obtained and written parental consent and verbal assent from the child was 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 PIS database.

Fetal measurements. These were obtained from paper records held in the mother's hospital notes. The crown rump length (CRL) was the first trimester measurement (i.e. ≤13

weeks gestation). In the second trimester (i.e. 14 to ≤28 weeks gestation) biparietal diameter (BPD) and femur length (FL) were measured. Fetal measurements were adjusted for gestation[25] and expressed as a z score to allow comparison between CRL, BPD, FL and spirometry. See online data supplement for 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 was used at 15 years (see online data supplement for full details)

Analysis. Characteristics of the different participation cohorts were described using number and percentage for categorical variables and mean and standard deviation (SD) for continuous outcomes (z-scores). Associations between fetal size and outcomes at 15 years were described using linear regression for continuous outcomes (e.g. lung function) and logistic regression for dichotomous outcomes (e.g. asthma yes or no). The on line data supplement describes covariates used. As previously[13,15] the first (i.e. crown rump length) 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 FEV_1, z-scores were different for those with and without PIS-confirmed prescription for asthma medications at 15 years. 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[27], SIMD) 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 adjusted for maternal asthma, maternal smoking (known to affect fetal size[28]) and SIMD. Gender was not used as an adjustment variable as it was used in the calculation of the z-score. Standard statistical software was used (IBM SPSS version 24.0.0 and SAS version 9.3).

RESULTS

Study participants

There were 1924 live born singleton infants and PIS provided asthma dispensing data in 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%) of participants at 15 years of whom 96 reported being prescribed asthma medications and medication categories were provided by 70 of these individuals of whom 37 were prescribed short acting beta agonist (SABA), 23 were prescribed inhaled corticosteroid (ICS) plus SABA and ten were prescribed ICS plus long acting beta agonist and/or leukotriene receptor antagonist. FEV_1 z score was available in 447 (23%), 431 (22%) and 514 (26%) study participants respectively. Table 1 presents details of those assessed at each age with the whole cohort and those for which dispensing data were available. Individuals where PIS data were available were representative of the original cohort for 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 with asthma dispensing data available from both questionnaire and PIS there were 670 (96%) concordant results (72 dispensed and 598

not dispensed asthma medications); there were 19 individuals at 15 years who reported being prescribed medications where PIS record indicated no prescription had been dispensed (false positive) and 9 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.

Relationship between fetal size and asthma dispensing data at fifteen years

The mean first trimester z score for fifteen year olds dispensed any asthma medication was -0.186 (SD 1.06, n=111) and was 0.025 (SD 0.99, n=954) for those not dispensed asthma medication. The odds ratio for being dispensed asthma medications at fifteen years were increased by 1.26 [95% confidence interval 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, table 2. There was no relationship between any fetal measurements and being dispensed eczema medications at 15 years, 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, (on line supplement table S1).

Relationship between fetal size and self-reported symptoms and spirometry at fifteen years

Reduced CRL and FL 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 hayfever or skin prick positivity (Table 3). Online supplement 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 FEF_{25-75} at 15 years of age (Table 3).

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

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 (-0.33, -0.06) between those who were and were not dispensed asthma medications at 15 years. When second trimester size was removed from the analysis, the mean reduction in CRL/FEV1 z-score was -0.23 (-0.38, -0.07). Figure 2 demonstrates that the reduction in the z-score for lung function (CRL and FL as a proxy) was significantly different between the two groups between 10weeks and 15 years, 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 becoming small children with small lungs.

DISCUSSION

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

to their fifteenth birthday had an overall reduction in fetal size and FEV_1 between ten weeks gestation and fifteen years of age (most notable at ten weeks and ten years of age). There was no association between fetal size and atopic outcomes including skin prick reactivity, hayfever and eczema. These observations suggests that mechanisms active in early pregnancy are associated with increased risk for asthma, and 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 fifteen years of age, consequently the associations with asthma dispensing should be minimally affected by bias due to non-participation. 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 non-linear 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) which suggests 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 five[13] and ten[15] years was limited to 501 and 350 study

participants respectively, and here we extend this association to fifteen years in 1170 study participants.

To 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 generalizable when there is the substantial drop out such as we experienced; the 61% drop out we experienced at 15 years 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 (odds ratio 1.55 versus 1.26). There was an apparent false positive result between self-reported asthma medication and 2nd 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 in less than perfect self-reporting of asthma medication use (PPV 79%).

In adult cohorts, there is evidence that drop out may not substantially bias outcomes[29,30] but in birth cohort studies, drop out does introduce considerable bias[21,31] and 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 that which fetal measurement is made is also important. Whilst first trimester CRL appears to be a viable surrogate for lung development in utero, second trimester bi-parietal diameter 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 which has described associations between fetal size and asthma outcomes at five and ten years[13,15]. The only other cohort to have linked fetal size to lung function has reported an association between reduced fetal weight and reduced lung function from the second trimester[14], but the same study by Sonnenschein *et al*[14] 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 which 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 though the life course, at least to 15 year 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] and this may explain why we saw no association between fetal size and spirometry at 15 years.

In the longitudinal analysis of fetal size and childhood FEV_1 there were reductions in first trimester size and lung function at ages ten years for those prescribed asthma medications compared to others, but there was no reduction in second trimester size nor spirometry at five 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 to femur and head size. First trimester fetal size is known to be a good predictor of birth weight[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 to second trimester fetal measurements[13,15].

There are some limitations to this study which should be considered when interpreting the results. First, we cannot be certain that some individuals who reported use of asthma medication which was not confirmed on the PIS record were not using inhalers intended for other family members; the PIS data capture prescribing in Scotland so it is unlikely that the participants had obtained medication from other countries. Second, like 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, whilst 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 and our findings therefore require replication elsewhere. Finally, fetal measurements were retrospectively collected from routine antenatal surveillance scans and this may have introduced greater inter-operator variability

for fetal measurements compared to 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 which 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.

At a Glance Commentary

Scientific Knowledge on the Subject. Birth cohort studies have demonstrated that birth weight is a determinant of lifelong respiratory well-being. Birth cohort studies are susceptible to drop out which may bias results obtained from those who continue to participate.

What This Study Adds to the Field. Reduced first trimester fetal size was associated with increased risk for asthma at 15 years of age. Asthma at 15 years of age was associated with reduced fetal size (an index of lung size) and reduced FEV_1 throughout childhood. We also demonstrate how a self-reported outcome leads to substantially different associations compared to routinely acquired outcome.

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Table 1. Details of the whole cohort, participants where data was available from prescribing information services (PIS) and where data were available from questionnaires and clinical assessments at ages five, ten and 15 years. NA=not assessed. IQR=interquartile range.

		Original population n=1924 unless stated	PIS data available at 15 years n=1699 unless stated	Questionnaire returned at 15 years n=747 unless stated
Male sex		50% (968)	50% (854)	46% (340)
Deprivation Quintile	SIMD* 1 (most deprived)	15% (284)	16% (266)	10% (72)
	SIMD2	9% (167)	9% (157)	8% (55)
	SIMD3	14% (268)	14% (238)	15% (105)
	SIMD4	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)
Mean CRL z score		0 (1.00) n=1206	0.005 (0.99) n=1170	0.034 (0.93) n=476
Mean BPD z score		0 (1.00) n=1676	0.002 (0.99) n=1622	0.020 (0.98) n=623
Mean FL z score		0.00 (1.00) n=1670	0.010 (1.00) n=1616	0.040 (1.02) n=622
Mean birth weight, kg (SD)		3.41 (0.61) n=1841	3.44 (0.56) n=1815	3.48 (0.56) n=691
Wheeze in the last 12 months, % (n)		NA	NA	15% (115/750)
Asthma diagnosed by physician, % (n)		NA	NA	20% (147/750)
Asthma medications		NA	NA	13% (96/748)
Current eczema, % (n)		NA	NA	16% (121/750)
Current hayfever, % (n)		NA	NA	36% (270/750)
Skin prick positive†, % (n)		NA	NA	44% (244/549)
Currently exposed to cigarette smoke, % (n)		NA	NA	5% (34/686)
Mean FEV_1 z score		NA	NA	-0.18 (1.05) n=514
Mean FEF_{25-75} z score		NA	NA	0.12 (0.96) n=515

*The Scottish Index of Multiple Deprivations. 1=most deprived quintile, 5=least deprived quintile[27]. †defined as a wheal ≥3mm to house dust mite, cat, timothy grass and egg.

Table 2. The relationship between first and second trimester fetal size and dispensed asthma and eczema medications at 15 years of age.

		1st trimester Mean Crown Rump Length Mean z score (SD)	2nd trimester Mean Biparietal Diameter Mean z score (SD)	2nd trimester Femur Length Mean z score (SD)
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)

Logistic regression adjusted for maternal smoking during pregnancy, maternal history of asthma.

Gestation and gender were included in calculation of z-scores, not included in logistic model.

SD = standard deviation; OR = odds ratio; CI = confidence interval. * p = 0.027

Table 3. Relationship between first and second trimester fetal size and self -eported symptom or respiratory outcome at 15 years of age per z score decrease in fetal measurement. *p<0.01 †p<0.05 and ≥0.01

Outcome	**1st trimester**	**2nd trimester**	
	Crown Rump Length OR[1] (95% CI)	**Biparietal Diameter OR[1] (95% CI)**	**Femur Length OR[1] (95% CI)**
Asthma at 15 years[2]	1.43 (1.12, 1.84)*	1.19 (0.96, 1.47)	1.35 (1.10, 1.65)*
Recent wheeze at 15[2]	1.31 (1.06, 1.61)†	1.03 (0.86, 1.23)	1.20 (1.01, 1.42)†
Receipt of asthma medications at 15[2]	1.55 (1.16, 2.08)*	1.20 (0.92, 1.56)	1.30 (1.03, 1.66)†
Current eczema at 15 [2]	1.07 (0.82, 1.42)	1.07 (0.85, 1.35)	0.97 (0.78, 1.20)
Current hayfever at 15[2]	1.22 (0.99, 1.50)	1.02 (0.87, 1.23)	1.08 (0.91, 1.27)
Atopy at 15[2]	1.08 (0.85, 1.38)	0.99 (0.80, 1.22)	1.00 (0.82, 1.21)
	estimate (95% CI)[3]	**estimate (95% CI)[3]**	**estimate (95% CI)[3]**
FEV_1 z score[4]	0.003 (-0.12, 0.13)	0.039 (-0.07, 0.15)	0.0 (-0.10, 0.10)
FEF_{25-75} z score[4]	-0.035 (-0.15, 0.08)	0.028 (-0.07, 0.12)	0.020 (-0.07, 0.11)

[1]OR for outcome per z score decrease in fetal measurement
[2]Logistic regression adjusted for maternal smoking during pregnancy, maternal history of asthma and gender
[3] coefficient per z-score reduction
[4] Linear regression adjusted for maternal smoking during pregnancy, maternal history of asthma (gender, age and height were included in calculation of z-scores and not included as covariates)
OR = odds ratio; CI = confidence interval. *p<0.01; †0.01<=p<0.05.

FIGURE LEGEND

Figure 1. A flow diagram showing the age at which data analysed in the present study were collected.

Figure 2. Graphical depiction which compares mean z scores of fetal measurements at 10 and 20 weeks gestation and the mean z scores of 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. 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 to the reference group.

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

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Take home message: Reduced first trimester size is associated with increased risk for asthma throughout childhood.

ABSTRACT

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

Methods. Fetal size in the first (T1) and second (T2) trimesters were ascertained by ultrasound scan. The primary outcome of being dispensed ≥1 asthma medication by the family doctor in the year before the 15th birthday was determined from routinely acquired dispensing data.

Results. Dispensing data were available in 1699 fifteen year olds (88% of the original cohort) and questionnaire data in 750 (39%). Each reduction in z score for T1 size was associated with increased odds for dispensed asthma medication at 15 years (OR = 1.26, 95 %CI (1.02, 1.54)) and self-reported use of asthma medications (OR=1.55, 95% CI (1.16, 2.08). Overall, there was reduced T1 and T2 size and reduced FEV_1 at ages 5, 10 and 15 for those dispensed asthma medications compared to those not dispensed asthma medications (p=0.003).

Conclusion. Antenatal factors which are active by T1 may contribute to respiratory wellbeing throughout childhood. Drop out from a birth cohort study can overestimate of the magnitude of any true association.

Key words: Asthma, Epidemiology, Child, Fetus, Longitudinal Studies

INTRODUCTION

Asthma and Chronic Obstructive Pulmonary Disease (COPD) are common respiratory conditions which are characterised by airflow obstruction. Childhood asthma symptoms usually develop in the preschool 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 since reduced birth weight is risk factor for COPD[6] and reduced lung function in adult life[7], whilst 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 post-natal 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 five[12,13], six[14] and ten years of age[15]. The relationship between fetal measurements and asthma symptoms is less consistent, with two cohorts observing associations between reduced fetal size[13,15] or change in fetal size[11,13,15] and increased risk for asthma symptoms but this was not replicated in a third[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; but also there is a recognised disconnect between reduced lung function and asthma symptoms[18] and thus a relationship may not be apparent in every population.

Lung function and the prevalence of asthma symptoms continue to change during the transition from childhood to adulthood[19,20], for example asthma prevalence rises in females but falls in males during puberty[20], and it is therefore important to replicate in adolescents any associations seen in childhood. Conventional follow up of birth cohorts requires making contact with the participants, however drop out of participants and ensuing biases[21], particularly during adolescence, are major limitations to birth cohort studies; a solution to this is the use of routinely acquired health care data[22]. Here we test the hypothesis that reduced fetal size is associated with increased risk for asthma. Our primary outcome was being dispensed ≥1 asthma medication 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 to those not dispensed ≥1 asthma medication 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. Figure one 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 online data supplement 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 previous assessments at five and ten years. 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 on line data supplement 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 ≥1 asthma medication in the 12 months prior to the fifteenth birthday using the same methodology previously described [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. On each of the three childhood assessments, separate medical ethics committee approval was obtained and written parental consent and verbal assent from the child was 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 PIS database.

Fetal measurements. These were obtained from paper records held in the mother's hospital notes. The crown rump length (CRL) was the first trimester measurement (i.e. ≤13

weeks gestation). In the second trimester (i.e. 14 to ≤28 weeks gestation) biparietal diameter (BPD) and femur length (FL) were measured. Fetal measurements were adjusted for gestation[25] and expressed as a z score to allow comparison between CRL, BPD, FL and spirometry. See online data supplement for 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 was used at 15 years (see online data supplement for full details)

Analysis. Characteristics of the different participation cohorts were described using number and percentage for categorical variables and mean and standard deviation (SD) for continuous outcomes (z-scores). Associations between fetal size and outcomes at 15 years were described using linear regression for continuous outcomes (e.g. lung function) and logistic regression for dichotomous outcomes (e.g. asthma yes or no). The on line data supplement describes covariates used. As previously[13,15] the first (i.e. crown rump length) 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 FEV_1, z-scores were different for those with and without PIS-confirmed prescription for asthma medications at 15 years. 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[27], SIMD) 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 adjusted for maternal asthma, maternal smoking (known to affect fetal size[28]) and SIMD. Gender was not used as an adjustment variable as it was used in the calculation of the z-score. Standard statistical software was used (IBM SPSS version 24.0.0 and SAS version 9.3).

RESULTS

Study participants

There were 1924 live born singleton infants and PIS provided asthma dispensing data in 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%) of participants at 15 years of whom 96 reported being prescribed asthma medications and medication categories were provided by 70 of these individuals of whom 37 were prescribed short acting beta agonist (SABA), 23 were prescribed inhaled corticosteroid (ICS) plus SABA and ten were prescribed ICS plus long acting beta agonist and/or leukotriene receptor antagonist. FEV_1 z score was available in 447 (23%), 431 (22%) and 514 (26%) study participants respectively. Table 1 presents details of those assessed at each age with the whole cohort and those for which dispensing data were available. Individuals where PIS data were available were representative of the original cohort for 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 with asthma dispensing data available from both questionnaire and PIS there were 670 (96%) concordant results (72 dispensed and 598

not dispensed asthma medications); there were 19 individuals at 15 years who reported being prescribed medications where PIS record indicated no prescription had been dispensed (false positive) and 9 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.

Relationship between fetal size and asthma dispensing data at fifteen years

The mean first trimester z score for fifteen year olds dispensed any asthma medication was -0.186 (SD 1.06, n=111) and was 0.025 (SD 0.99, n=954) for those not dispensed asthma medication. The odds ratio for being dispensed asthma medications at fifteen years were increased by 1.26 [95% confidence interval 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, table 2. There was no relationship between any fetal measurements and being dispensed eczema medications at 15 years, 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, (on line supplement table S1).

Relationship between fetal size and self-reported symptoms and spirometry at fifteen years

Reduced CRL and FL 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 hayfever or skin prick positivity (Table 3). Online supplement 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 FEF_{25-75} at 15 years of age (Table 3).

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

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 (-0.33, -0.06) between those who were and were not dispensed asthma medications at 15 years. When second trimester size was removed from the analysis, the mean reduction in CRL/FEV1 z-score was -0.23 (-0.38, -0.07). Figure 2 demonstrates that the reduction in the z-score for lung function (CRL and FL as a proxy) was significantly different between the two groups between 10weeks and 15 years, 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 becoming small children with small lungs.

DISCUSSION

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

to their fifteenth birthday had an overall reduction in fetal size and FEV_1 between ten weeks gestation and fifteen years of age (most notable at ten weeks and ten years of age). There was no association between fetal size and atopic outcomes including skin prick reactivity, hayfever and eczema. These observations suggests that mechanisms active in early pregnancy are associated with increased risk for asthma, and 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 fifteen years of age, consequently the associations with asthma dispensing should be minimally affected by bias due to non-participation. 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 non-linear 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) which suggests 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 five[13] and ten[15] years was limited to 501 and 350 study

participants respectively, and here we extend this association to fifteen years in 1170 study participants.

To 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 generalizable when there is the substantial drop out such as we experienced; the 61% drop out we experienced at 15 years 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 (odds ratio 1.55 versus 1.26). There was an apparent false positive result between self-reported asthma medication and 2nd 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 in less than perfect self-reporting of asthma medication use (PPV 79%).

In adult cohorts, there is evidence that drop out may not substantially bias outcomes[29,30] but in birth cohort studies, drop out does introduce considerable bias[21,31] and 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 that which fetal measurement is made is also important. Whilst first trimester CRL appears to be a viable surrogate for lung development in utero, second trimester bi-parietal diameter 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 which has described associations between fetal size and asthma outcomes at five and ten years[13,15]. The only other cohort to have linked fetal size to lung function has reported an association between reduced fetal weight and reduced lung function from the second trimester[14], but the same study by Sonnenschein *et al*[14] 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 which 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 though the life course, at least to 15 year 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] and this may explain why we saw no association between fetal size and spirometry at 15 years.

In the longitudinal analysis of fetal size and childhood FEV_1 there were reductions in first trimester size and lung function at ages ten years for those prescribed asthma medications compared to others, but there was no reduction in second trimester size nor spirometry at five 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 to femur and head size. First trimester fetal size is known to be a good predictor of birth weight[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 to second trimester fetal measurements[13,15].

There are some limitations to this study which should be considered when interpreting the results. First, we cannot be certain that some individuals who reported use of asthma medication which was not confirmed on the PIS record were not using inhalers intended for other family members; the PIS data capture prescribing in Scotland so it is unlikely that the participants had obtained medication from other countries. Second, like 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, whilst 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 and our findings therefore require replication elsewhere. Finally, fetal measurements were retrospectively collected from routine antenatal surveillance scans and this may have introduced greater inter-operator variability

for fetal measurements compared to 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 which 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.

At a Glance Commentary

Scientific Knowledge on the Subject. Birth cohort studies have demonstrated that birth weight is a determinant of lifelong respiratory well-being. Birth cohort studies are susceptible to drop out which may bias results obtained from those who continue to participate.

What This Study Adds to the Field. Reduced first trimester fetal size was associated with increased risk for asthma at 15 years of age. Asthma at 15 years of age was associated with reduced fetal size (an index of lung size) and reduced FEV_1 throughout childhood. We also demonstrate how a self-reported outcome leads to substantially different associations compared to routinely acquired outcome.

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Table 1. Details of the whole cohort, participants where data was available from prescribing information services (PIS) and where data were available from questionnaires and clinical assessments at ages five, ten and 15 years. NA=not assessed. IQR=interquartile range.

		Original population n=1924 unless stated	PIS data available at 15 years n=1699 unless stated	Questionnaire returned at 15 years n=747 unless stated
Male sex		50% (968)	50% (854)	46% (340)
Deprivation Quintile	SIMD* 1 (most deprived)	15% (284)	16% (266)	10% (72)
	SIMD2	9% (167)	9% (157)	8% (55)
	SIMD3	14% (268)	14% (238)	15% (105)
	SIMD4	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)
Mean CRL z score		0 (1.00) n=1206	0.005 (0.99) n=1170	0.034 (0.93) n=476
Mean BPD z score		0 (1.00) n=1676	0.002 (0.99) n=1622	0.020 (0.98) n=623
Mean FL z score		0.00 (1.00) n=1670	0.010 (1.00) n=1616	0.040 (1.02) n=622
Mean birth weight, kg (SD)		3.41 (0.61) n=1841	3.44 (0.56) n=1815	3.48 (0.56) n=691
Wheeze in the last 12 months, % (n)		NA	NA	15% (115/750)
Asthma diagnosed by physician, % (n)		NA	NA	20% (147/750)
Asthma medications		NA	NA	13% (96/748)
Current eczema, % (n)		NA	NA	16% (121/750)
Current hayfever, % (n)		NA	NA	36% (270/750)
Skin prick positive†, % (n)		NA	NA	44% (244/549)
Currently exposed to cigarette smoke, % (n)		NA	NA	5% (34/686)
Mean FEV_1 z score		NA	NA	-0.18 (1.05) n=514
Mean FEF_{25-75} z score		NA	NA	0.12 (0.96) n=515

*The Scottish Index of Multiple Deprivations. 1=most deprived quintile, 5=least deprived quintile[27]. †defined as a wheal ≥3mm to house dust mite, cat, timothy grass and egg.

Table 2. The relationship between first and second trimester fetal size and dispensed asthma and eczema medications at 15 years of age.

		1st trimester Mean Crown Rump Length Mean z score (SD)	2nd trimester Mean Biparietal Diameter Mean z score (SD)	2nd trimester Femur Length Mean z score (SD)
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)

Logistic regression adjusted for maternal smoking during pregnancy, maternal history of asthma.

Gestation and gender were included in calculation of z-scores, not included in logistic model.

SD = standard deviation; OR = odds ratio; CI = confidence interval. * p = 0.027

Table 3. Relationship between first and second trimester fetal size and self -eported symptom or respiratory outcome at 15 years of age per z score decrease in fetal measurement. *p<0.01 †p<0.05 and ≥0.01

Outcome	**1st trimester**	**2nd trimester**	
	Crown Rump Length OR[1] (95% CI)	**Biparietal Diameter OR[1] (95% CI)**	**Femur Length OR[1] (95% CI)**
Asthma at 15 years[2]	1.43 (1.12, 1.84)*	1.19 (0.96, 1.47)	1.35 (1.10, 1.65)*
Recent wheeze at 15[2]	1.31 (1.06, 1.61)†	1.03 (0.86, 1.23)	1.20 (1.01, 1.42)†
Receipt of asthma medications at 15[2]	1.55 (1.16, 2.08)*	1.20 (0.92, 1.56)	1.30 (1.03, 1.66)†
Current eczema at 15 [2]	1.07 (0.82, 1.42)	1.07 (0.85, 1.35)	0.97 (0.78, 1.20)
Current hayfever at 15[2]	1.22 (0.99, 1.50)	1.02 (0.87, 1.23)	1.08 (0.91, 1.27)
Atopy at 15[2]	1.08 (0.85, 1.38)	0.99 (0.80, 1.22)	1.00 (0.82, 1.21)
	estimate (95% CI)[3]	**estimate (95% CI)[3]**	**estimate (95% CI)[3]**
FEV_1 z score[4]	0.003 (-0.12, 0.13)	0.039 (-0.07, 0.15)	0.0 (-0.10, 0.10)
FEF_{25-75} z score[4]	-0.035 (-0.15, 0.08)	0.028 (-0.07, 0.12)	0.020 (-0.07, 0.11)

[1]OR for outcome per z score decrease in fetal measurement
[2]Logistic regression adjusted for maternal smoking during pregnancy, maternal history of asthma and gender
[3] coefficient per z-score reduction
[4] Linear regression adjusted for maternal smoking during pregnancy, maternal history of asthma (gender, age and height were included in calculation of z-scores and not included as covariates)
OR = odds ratio; CI = confidence interval. *p<0.01; †0.01<=p<0.05.

FIGURE LEGEND

Figure 1. A flow diagram showing the age at which data analysed in the present study were collected.

Figure 2. Graphical depiction which compares mean z scores of fetal measurements at 10 and 20 weeks gestation and the mean z scores of 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. 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 to the reference group.

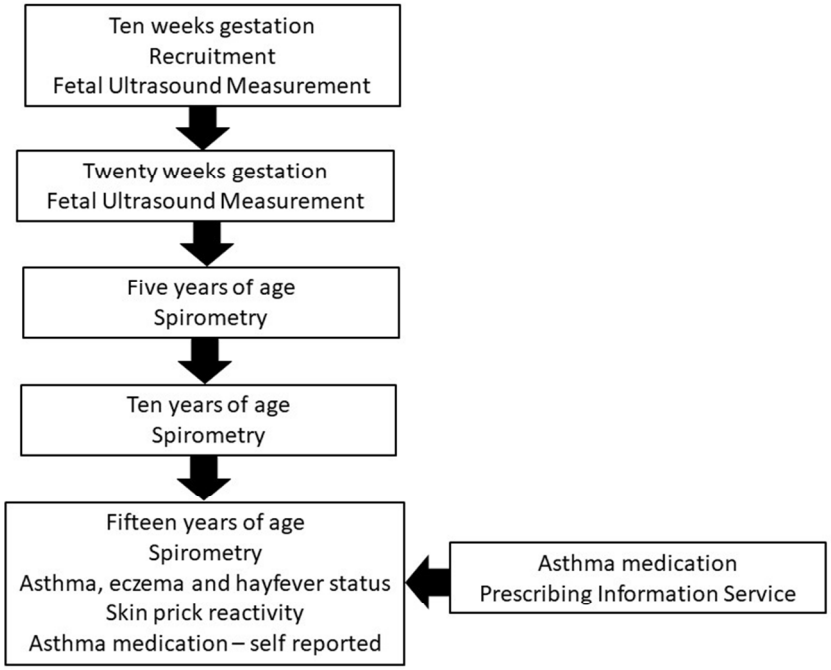

Figure 1. A flow diagram showing the age at which data analysed in the present study were collected.

254x190mm (96 x 96 DPI)

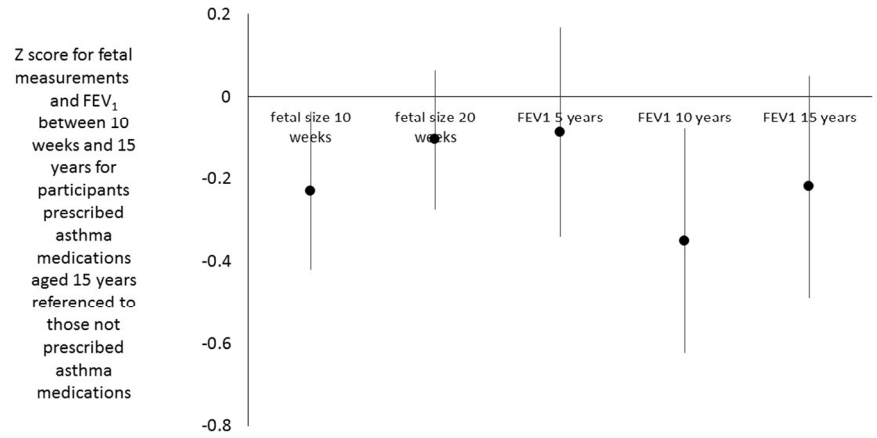

Figure 2. Graphical depiction which compares mean z scores of fetal measurements at 10 and 20 weeks gestation and the mean z scores of FEV1 at 5, 10 and 15 years in children dispensed asthma medications at 15 years of age with reference to children not dispensed asthma medications at 15. The longitudinal analysis (a linear mixed effects model) considered z scores of fetal measurements and FEV1, and demonstrated an overall reduction in fetal size/FEV1 z score of 0.20 (95% CI -0.33, -0.06) p = 0.003 between those dispensed asthma medications compared to the reference group.

338x190mm (96 x 96 DPI)

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

On line supplement

METHODS

Characteristics of participants relative to the general population

We have previously described that 74% of those invited to participate were enrolled and that participants were mostly representative of the general population although they were slightly older (29.6 versus 29.1 years), had a lower prevalence of smoking (19% versus 24%) and more likely to have a partner with a non-manual occupation (46% versus 44%) [1].

Questions asked at 15 years

The questionnaire was designed to be completed by the participant. Wheeze was defined as an affirmative response to the question "have you had wheezing or whistling in the chest in the last 12 months?" Asthma was defined as a positive response to the questions "have you ever suffered from asthma?", "was this confirmed by a doctor?" and "have you had asthma in the last 12 months?" Participants were also asked "have you been prescribed medicines/inhalers for asthma in the last 12months?". Smoking exposure at 15 years was ascertained from a positive response to the question "Does anyone smoke in the house in which you spend the majority of your time?"

Gestational accuracy and reproducibility of fetal measurements

Gestation was determined from the date of the maternal last menstrual period (LMP) unless gestation by CRL was >14 days different to LMP, in which case the gestation by CRL was used. The apparatus used for fetal ultrasound measurements have been previously described [2,3] and inter operator variability for first trimester measurements is 0.89-0.94 (expressed as intraclass correlation coefficients)[4] and for second trimesters is typically 0.75-0.85 (expressed as percentage agreement)[5].

Prescribing Information Service

Asthma medications (as coded in the British National Formulary, version 69, March 2015-Sept 2015) included short acting beta agonists (3.1.1 including salbutamol and turbutaline sulfate), inhaled

corticosteroids (3.2 including budesonide, beclomethasone diproprionate, ciclesonide, fluticasone and mometasone), long acting beta agonists (3.1.1, including salmeterol, formoterol), leukotriene receptor antagonists (3.3.2 including montelukast and zafirlukast) and theophylline (3.1.3). Prescribing for eczema medications including topical emollients and barrier preparations (13.2 an extensive list of preparations), corticosteroids (13.4 including hydrocortisone, beclomethasone diproprionate, betamethasone esters, clobetasol proprionate and clobetasol butyrate), oral retinoids (13.5.1 including ichthammol and alitretinoin) was also determined for cohort members.

Methodology for spirometry and skin prick reactivity

Spirometry was measured at ages five, ten and fifteen years using the same apparatus with visual incentive (21/20 Vitalograph, Bucks, UK) in accordance with international guidelines[6] and expressed as z score standardised against an international reference[7]. The skin prick test was used to determine skin prick reactivity to common allergens [8]. Reactivity to house dust mite, cat, timothy grass and egg was determined at all three assessments and to dog and peanut at ten years of age. Positive and negative controls were used. All allergens and controls provided by ALK Abello (Northants, UK). Atopy was defined as a weal with a maximum diameter of ≥3mm to any allergen or in cases of dermatographism, a weal greater than the positive control.

~~**Analysis**~~

~~Models adjusted for maternal asthma, maternal smoking and deprivation (as determined by the Scottish Index of Multiple Deprivations, SIMD). Gender was not used as an adjustment variable as it was used in the calculation of the z-score.~~

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