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Antenatal size, early childhood growth, and asthma within a cohort created by data linkage

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Abstract

Introduction: The gestation when small for gestational age (SGA) is first associated with asthma is not well understood. Here, we use routinely acquired data from 10 weeks gestation to up to 28 years of age to test the hypothesis that SGA before birth is associated with an increased risk for asthma in a large population born between 1987 and 2015.

Methods: Databases were linked to produce a single database that held antenatal fetal ultrasound measurements; maternal characteristics; birth measurements; childhood anthropometric measurements at age 5 years; hospital admission data (1987–2015); and family doctor prescribing (2009–2015). Asthma admission and receipt of any asthma medications were the outcomes. Analyses related single and then multiple anthropometric measurements to asthma outcomes.

Results: Outcome data were available for 63,930 individuals. Increased length in the first-trimester size was associated with a reduced odds ratio (OR) for asthma admission of 0.991 [0.983, 0.998] per mm increase and also a shorter time to first admission, with a hazard ratio risk of 0.987 [0.980, 0.994] per mm increase. Independent of all earlier measurements, increased height at 5 years (available in a subset of 15,760) was associated with reduced OR for an asthma admission, with OR of 0.874 [0.790, 0.967] per *z* score. Longitudinal measurements of weight were not related to asthma outcomes.

Conclusions: Longer first-trimester length is associated with more favorable asthma outcomes, and subsequently, increased height in childhood is also independently associated with more favorable asthma outcomes. Interventions that reduce SGA and encourage healthy postnatal growth might improve asthma outcomes.

KEYWORDS

asthma, fetus, growth, information storage and retrieval, longitudinal studies

1 | INTRODUCTION

Small for gestational age (SGA) at birth is a risk factor for asthma[1] and chronic obstructive pulmonary disease[2] and other noncommunicable diseases (NCDs), including obesity,[3] ischemic heart disease,[4] and type II diabetes mellitus.[5] These observations[1–5] suggest that the factors active in antenatal development have life-long implications for health and well-being. Hypotheses explaining the relationship between antenatal life and NCDs, including the fetal origins hypothesis,[5] developmental plasticity,[6] and predictive adaptive responses,[7] propose that antenatal cues trigger a change in fetal growth which confers a survival advantage in early life at the expense of increased morbidity in later life.

In support of the "fetal origins" concept, there is evidence that maternal exposures during pregnancy, including smoking[8] and ambient air exposures,[9] are linked to SGA in antenatal life, and there is also literature describing links between SGA before birth and increased risk for NCDs in early childhood, including asthma.[10] The relationship between fetal size and asthma is limited to a small number of cohorts with relatively short duration of follow-up, and two find an association between reduced fetal size and increased risk for asthma.[11,12] In a third birth cohort, there was no association between fetal size and asthma symptoms,[13] but in this third birth cohort there was a relationship between reduced fetal size and increased airway resistance.[14]

There are several challenges linking antenatal SGA to asthma outcomes, including the availability of antenatal fetal measurements, the need to wait for birth cohort participants to reach an age when asthma is present, recruiting an adequate size population, recruitment bias, and loss to follow-up.[15] We have addressed these challenges by linking routinely acquired clinical data to create a "virtual" birth cohort. We explored the relationship between SGA up to and including birth and risk for asthma outcomes in a large population with an age ≤28 years. We also determined whether any relationship between SGA up to and including birth was independent of later antenatal and postnatal growth (the latter within a subset where postnatal growth measurements were available).

2 | METHODS

2.1 | Study design

This study linked databases holding the following routinely acquired data: fetal and newborn anthropometric measurements plus maternal characteristics; height and weight measurements in 5-year-olds; family doctor prescribing beginning in 2009; details of hospital admissions beginning in 1987.[16] Linkage was through a common identifier (the community health index number). Linkage was completed in 2015, meaning that the oldest participant was aged no more than 28 years. An earlier publication describes the linkage of some databases linked in this study: the Aberdeen Maternal and Neonatal Databank (AMND) and Study of Trends in Obesity in North East Scotland (STONES) databases.[17] Approval for the linkage was provided by the Public Benefit and Privacy Panel for Health and Social Care (1516-0387) and the North of Scotland Research Ethics Committee (IRAS 202351).

2.2 | Setting

North East Scotland.

2.3 | Participants

All individuals were scheduled for delivery at Aberdeen Maternity Hospital between 1987 and 2015.

2.4 | Variables

The definitions of asthma were asthma admission to hospital (1987–2015), being prescribed any asthma medication (2009–2015), and being prescribed an inhaled corticosteroid (2009–2015). In addition to these three definitions, we also had time at first asthma admission as a fourth outcome. Since antenatal and birth details were known from 1987 and medication data from 2009, the age at first prescription was considerably older than the age at first admission. Predictors were antenatal and birth measurements. Confounding variables were sex, maternal smoking, maternal height, maternal asthma, deprivation, and parity.

2.5 | Data sources

2.5.1 | The Aberdeen Maternity and Neonatal Databank (AMND)

Maternal and fetal data have been collected in the AMND since 1950.[18] Routine antenatal ultrasound scanning was introduced in Aberdeen in 1987, and data were included from this time onwards. Available maternal variables were self-reported smoking status in early pregnancy; height; weight (results collected after 16 weeks gestation were excluded from the analysis to avoid healthy gestational weight gain being confused with overweight or obese); parity; and self-reported asthma (i.e., all ICD-9 codes beginning 493). Socioeconomic status was determined using the Carstairs index,[19] which has a score between 1 and 7 (7 being most deprived). In North East Scotland, there are no communities with a score of 7. First- and second-trimester ultrasound scans are offered to all mothers. Third-trimester ultrasound scans are only arranged for a subset with obstetric indications; for example, breech presentation. In the first trimester, crown–rump length (CRL) was measured. In the second and third trimesters, biparietal diameter (BDP), femur length (FL), and abdominal circumference (AC) were determined. Fetal measurements were made with ATL (Ultramark 4A) or Toshiba (SSA-240A or SSA-340A). Intraclass correlation coefficients for interoperator first-trimester measurements is 0.89–0.94,[20] and percentage agreement for second

trimesters is 0.75–0.85.[21] Scatter plots comparing measurement against gestation were used to remove outlying results. The method of Hadlock was used to determine the estimated fetal weight (EFW).[22] A standard methodology was used to determine *z* scores of fetal measurements adjusting for gestation.[23] The AMND provided a birth weight *z* score standardized for gestation, sex, and birth order. *Z* scores for crown–heel length (CHL) and occipito-frontal circumference at birth were derived using the AMND population adjusting for gestation. Multiple pregnancies were excluded since it is not possible to link fetal measurements to postnatal measurements.

2.5.2 | Study of Trends in Obesity in North East Scotland (STONES)

Height and weight measurements are collected at a mean age of 5.5 years when children first attend school.[24] Data from children born in 1987 onward were used. Measurements are standardized to the UK 1990 cohort[25] and International Obesity Task Force definitions[26] of thin, healthy weight, overweight, and obese were used.

2.5.3 | Prescribing information services (PIS)

This details all medications prescribed by family doctors in Scotland beginning in 2009.[27] In Scotland, the only means to obtain medication for asthma is through a doctor's prescription. British National Formulary codes[28] were used to identify prescriptions for short-acting beta agonists, inhaled corticosteroids (ICS), long-acting beta agonists, and leukotriene receptor antagonists.

2.5.4 | Standard morbidity record 1 (SMR01)

From this national resource[16] the date of any asthma admission (using ICD-9 codes) between 1987 and 2015 was identified.

2.6 | Bias

No efforts were made to address potential source of bias.

2.7 | Study size

This was determined by the number of individuals scheduled to be delivered at Aberdeen Maternity Hospital.

2.8 | Quantitative variables

All continuous variables were analyzed as continuous variables. CRL was expressed as quintiles for visual purposes.

2.9 | Analysis

2.9.1 | Relating single anthropometric measurements to asthma outcomes

Mean fetal, neonatal, and childhood measurements were compared between groups stratified by asthma outcome (yes/no). General linear models were created to describe the difference in anthropometric measurements between groups defined by asthma outcome adjusting for sex, gestational age at scan/birth, offspring age in 2015, maternal smoking, maternal asthma, socioeconomic status, and parity. Maternal height was included for analyses which also included fetal indices of length and maternal weight for analyses including indices of fetal weight.

2.9.2 | Relating multiple anthropometric measurements to asthma outcomes

To recognize the co-linearity in measurements of length or height made within an individual at different time points, longitudinal analysis was used to determine whether associations between size and asthma outcomes at different ages were independent of each other. Mixed-level models (with binomial distribution) related anthropometric measurements in the first and second trimesters, birth, and 5 years to asthma outcomes (yes/no), adjusting for sex, maternal smoking, maternal height, maternal asthma, deprivation, and parity. Time was a categorical variable corresponding to the first, second, and third trimesters, birth, and 5 years of age. Third-trimester measurements were only made for obstetric reasons (which could include SGA) and were not included in the main analyses but were included in additional analyses reported in the supplement. Subgroup analyses repeated the analysis of prescribed information (i) restricted to individuals who were born between 2008 and 2015 (i.e., all of whom would have PIS data available) and also between 1993–2015, 1998–2015 and 2003–2015 (i.e., increasingly enriched with individuals with complete PIS data) (ii) restricted to individuals with more than 2–6 years ICS treatment prescribed between 2009 and 2015 (to determine whether associations differed when ICS prescribing was increasingly complete). Further subgroup analyses were carried out (i) after excluding those born prematurely (i.e., <37 completed gestational weeks) and/or with low birth weight (i.e., <2.5 kg) and (ii) including only those who were overweight or obese at 5 years of age.

2.9.3 | Survival analysis

Cox proportionate hazards models were created to relate anthropometric measurements to time to first asthma outcome with adjustment for sex, gestational age at scan/birth, maternal smoking, maternal height, maternal asthma, socioeconomic status, and parity. Standard statistical software was used (IBM SPSS version 25). Given

the relatively large sample size, a p value of <0.025 was assumed to be significant (instead of the more usual 0.05).

3 | RESULTS

3.1 | Participants and descriptive data

Asthma outcomes were available for 63,930 individuals, in whom anthropometric data were available in the following numbers: 38,516 (60%) in the first trimester; 37,444 (59%) in the second trimester; 22,554 (35%) in the third trimester; 63,923 (100%) at birth; and 15,760 (25%) at 5 years (Table 1). Supporting Information: Figure 1 also presents the numbers of individuals for whom data were available. Maternal asthma, age, and offspring sex data were complete, smoking status was missing in 1.5% and deprivation in 18%. Table 1 presents the characteristics of all 63,930 individuals and the subgroup of 15,760 where measurements at 5 years were available. Individuals for whom 5-year-old data were available were more likely to have mothers with asthma, less likely to be from deprived communities, and were younger in 2015 compared with those where height and weight data were not available at 5 years (Table 1). Supporting Information: Table 1 compares the characteristics of all individuals and the 954 individuals whose anthropometric measurements were available in all three trimesters, birth, and at 5 years.

3.2 | Outcome data

There were 3472 (5%) individuals with at least one admission for asthma, and the median age of first admission (interquartile range, IQR) was 2 years (1,4). There were 11,799 (18%) individuals with at least one asthma medication prescribed between 2009 and 2015, and the median (IQR) age of the first asthma medication prescription during this period was 17 years (9, 21). There were 11,557 prescribed short-acting beta agonists (1239 individuals prescribed in each of the 7 years where data were available), 6288 ICS (median [IQR] age 17 [10, 21], prescribed for all 7 years in 888 individuals), 870 leukotriene receptor antagonist (56 for all 7 years), and 195 prescribed long-acting beta agonists (eight for all 7 years). Asthma medications were prescribed between 2009 and 2015 in 2333 (67%) of those with an asthma admission between 1987 and 2015.

3.3 | Main results

3.3.1 | Relating single anthropometric measurements to asthma outcomes

Asthma admissions

The odds ratio (OR) (95% confidence interval [CI]) for an asthma admission reduced with increasing first trimester length reducing second trimester length, increasing birth length and also with increased weight at birth. The OR were 0.991 [0.983, 0.998] per mm increase in CRL ($p = 0.017$), 1.006 [1.001, 1.012] ($p = 0.021$) per mm increase in FL, 0.979 [0.960, 0.998] $p = 0.032$ per cm increase in CHL, and 0.988 [0.979, 0.996] $p = 0.004$ per cm increase in height at 5 years. The OR were 0.887 [0.800, 0.982] $p = 0.021$ per kg increase in birth weight. Other length and weight measurements were not different between those who had an admission compared with those who did not (Table 2).

Asthma medications

The OR for any asthma medications prescribed between 2009 and 2015 reduced with increasing weight and length at birth; OR were 0.891 [0.841, 0.943] $p < 0.001$ per kg increase in birth weight and 0.976 [0.965, 0.988] $p < 0.001$ per cm increase in CHL (Table 2). Supporting Information: Table 2 compares differences in anthropometric measurements between those who did and did not have any asthma medication stratified by completeness of the available PIS data; increased birth weight was associated with reduced OR for being prescribed asthma medications among those born between 2003 and 2015, 1998 and 2015, and 1993 and 2015.

The OR for any inhaled corticosteroid prescription was 0.907 [0.841, 0.977] $p = 0.011$ per kg increase in birth weight and 0.978 [0.964, 0.992] $p = 0.003$ per cm increase in CHL (Table 2). Supporting Information: Table 3 compares differences in anthropometric measurements between those who never had ICS prescribed 2009–2015 against those who had ICS prescribed in more than 2–6 years between 2009–2015; increased birth weight was associated with reduced OR for being prescribed ICS for more than 2 or 3 years.

Supporting Information: Table 4 shows how the exclusion of those born <37 weeks and with birth weight <2.5 kg did not substantially change the associations shown in Table 2. Supporting Information: Table 5 shows mean (unadjusted) absolute measurements of other anthropometric measurements not previously described, that is, head size and third-trimester measurements, stratified by asthma outcomes; there were no differences in these measurements with stratification by asthma outcomes.

3.3.2 | Relating multiple anthropometric measurements to asthma outcomes

Asthma admissions

When first-trimester length (CRL) was included (as a reference), second-trimester length (FL) and length at birth were not associated with altered risk for an asthma admission, but increasing height at 5 years was independently associated with reduced risk for asthma admission (OR 0.874 [0.790, 0.967] $p = 0.009$) (Table 3).

Asthma medications

With second-trimester weight as the reference (no index of weight was available in the first trimester), increasing weight at birth (but not 5 years)

TABLE 1 Comparison of maternal and fetal characteristics for the whole cohort (n = 63,930) and the subgroup where anthropometric measurements were available at 5 years of age.

Characteristic		Whole cohort (i.e., hospital admission and prescribing details available) n = 63,930	Data available at 5 years[a] (n = 15,760)
Mean maternal age (SD)		28.1 (5.4)	28.9 (5.6)
Maternal smoking	Current	25% (15,906/62,981)	22% (3487/15,542)
	Ex-smoker	6% (3907/62,981)	7% (1151/15,542)
	Nonsmoker	68% (43,168/62,981)	70% (10,904/15,542)
Parity	0	47% (29,955/63,929)	48% (7621/15,760)
	1	35% (22,552/63,929)	35% (5559/15,760)
	2	13% (8124/63,929)	11% (1799/15,760)
	≥3	5% (3298/63,929)	5% (781/15,760)
Deprivation category[a]	1 (least)	16% (8470/52,689)	21% (3308/15,439)
	2	30% (15,640/52,689)	32% (4885/15,439)
	3	18% (9734/52,689)	15% (2242/15,439)
	4	19% (9808/52,689)	16% (2432/15,439)
	5	10% (5385,52,689)	7% (1053/15,439)
	6 (most)	7% (3652/52,689)	10% (1519/15,439)
Mean maternal BMI (SD), kg/m^2		24.7 (4.7) n = 49,878	25.2 (5.2) n = 14,139
Maternal asthma		9% (5638/63,930)	13% (1999/15,760)
Male sex		51% (32,781/63,930)	51% (7979/15,763)
Mean first-trimester crown–rump length, mm (SD)		51.8 (17) n = 38,516	52.4 (15.8) n = 11,608
Mean second-trimester femur length, mm (SD)		33.5 (9.1) n = 37,444	33.9 (7.4) n = 12,458
Mean second-trimester estimated fetal weight, g (SD)		538 (325) n = 13,418	496 (290) n = 6864
Mean third-trimester femur length, mm (SD)		68.3 (6.0) n = 22,554	67.9 (5.9) n = 5230
Mean third-trimester estimated fetal weight, g (SD)		2812 (682) n = 12,469	2766 (679) n = 4473
Mean crown–heel length (birth), cm (SD)		49.8 (2.6) 63,291	49.8 (2.6) n = 15,690
Mean birth weight, kg (SD)		3.38 (0.56) n = 63,923	3.39 (0.57) n = 15,760
Gestation <37 weeks and/or birth weight <2.5 kg		6% (3928/63,930)	7% (1036/15,760)
Age in 2015	Under 5 years	5% (2961/63,930)	5% (856/15,760)
	5- < 10.0 years	13% (8453/63,930)	40% (6281/15,760)
	10- < 15.0 years	14% (9167/63,930)	18% (2867/15,760)
	15- < 20.0 years	15% (9753/63,930)	29% (4497/15,760)
	20- < 25.0 years	38% (24,438/63,930)	8% (1259/15,760)
	≥25.0 years	14% (9152/63,930)	0
Mean height aged 5 years, cm (SD)		114 (7) n = 15,760	
Mean z score height 5 years (SD)		0.10 (1.02) n = 15,760	
Mean weight aged 5 years, kg (SD)		20.9 (4.2) n = 15,760	
Mean z score weight 5 years (SD)		0.23 (1.09) n = 15,760	
Admitted to hospital for asthma ever		5% (3472/63,930)	3% (498/15,760)
Any asthma prescriptions 2009–2015		18% (11,799/63,930)	21% (3386/15,760)

(Continues)

TABLE 1 (Continued)

Characteristic	Whole cohort (i.e., hospital admission and prescribing details available) *n* = 63,930	Data available at 5 years[a] (*n* = 15,760)
Any short-acting beta agonist prescription	18% (11,557/63,930)	21% (3305/15,760)
Any inhaled corticosteroid prescription	10% (6288/63,930)	11% (1709/15,760)

Note: *$p < 0.025$ for all characteristics compared with the whole cohort except sex. The large number of individuals in the linked data set meant that small differences of doubtful relevance would be highly significant.

Abbreviations: BMI, body mass index; SD, standard deviation.

[a]The Carstairs method has seven categories. There are no communities with the highest deprivation score (seven) in North East Scotland.

was associated with reduced OR for being prescribed asthma medications but did not reach our threshold for significance (OR 0.970 per *z* score [0.943, 0.988] $p = 0.037$) (Table 4). This relationship remained below the $p = 0.025$ threshold when third-trimester weight was included; Supporting Information: Table 6. When first-trimester length was included, only increased weight at 5 years was independently associated with increased OR for being prescribed asthma medications (OR 1.051 [0.013, 1.090] $p = 0.008$); Supporting Information: Table 6. Indices of length were not associated with altered OR for being prescribed asthma medications with first-trimester length as the reference (Table 3) and also with second-trimester length as the reference; Supporting Information: Table 7. When OR for being prescribed asthma medications was limited to those born after 2003 and separately to those who were overweight or obese at age 5 years, a similar magnitude of OR was obtained but without achieving significance (Supporting Information: Tables 8 and 9).

In the models including the whole data set where asthma admission and asthma medications were the outcomes, male sex, maternal asthma, reducing maternal height, maternal smoking, increasing deprivation, and being firstborn were all associated with increased risk for the outcome.

3.4 | Antenatal and birth measurements and time to first asthma admission—Survival analysis

Decreased CRL was associated with a younger age at first admission (hazard ratio, 0.987 per mm [95% CI 0.980, 0.994] $p = 0.001$), that is, the risk of admission at any particular point in time increases by 1.3% for each mm decrease in CRL. Figure 1 shows how the age at first asthma admission was the youngest for those in the lowest quintile for CRL *z* score. Other indices of antenatal and birth length were not related to the risk of admission. The survival analysis for time to first prescription was limited to those born 2003–2015, and no antenatal or birth measurements were linked to this outcome.

4 | DISCUSSION

Our manuscript describes associations between anthropometric measurements between the first trimester and 5 years of age and postnatal asthma outcomes. Increasing length in the first trimester and at 5 years of age were independently associated with more favorable asthma outcomes. The relationship between weight and asthma outcomes was less clear, in part due to no available first-trimester estimate of weight, and there was evidence that reduced weight at birth or increased weight at 5 years was associated with increased risk for asthma. Future work could determine whether asthma risk may be reduced by interventions in early pregnancy (or before) aimed at reducing SGA.

This paper also highlights the potential and limitations of using the linkage of routinely acquired data to create a large "virtual cohort" to explore asthma outcomes over the life course through to adulthood. Our findings suggest that the linkage of routinely acquired data might usefully complement results using other epidemiological approaches, for example, traditional birth cohort studies.

Data linkage using routinely acquired data sets has been used to relate fetal size to childhood obesity,[17] antenatal maternal air pollution to fetal size,[29] and childhood obesity to orthopedic outcomes.[30] The strengths of this methodology include creating a relatively large sample size that reaches an older age substantially more quickly than a traditional cohort study. The limitations to data linkage studies using routinely acquired data include data being missing and not randomly missing, outcomes being inferred by proxy, and being reliant on historical definitions. There is no definition of asthma and for this study, we used receipt of asthma medications (2009–2015) and asthma admission (1987–2015) as proxies for asthma. Neither is an infallible proxy since we have no knowledge of asthma medications before 2009, medications may have been prescribed for non-asthmatic symptoms, and not all individuals with asthma will be admitted for an asthma attack. The potential for misclassification bias due to reliance on routinely acquired data is likely to weaken the associations described. Such misclassification is also likely to be greater in younger children, for example, under 3-year-olds, where an asthma diagnosis can be less secure, and also for asthma admissions since symptoms of acute lower respiratory tract infections and acute asthma are very similar.

A further limitation of data linkage studies is that despite a relatively large whole population sample size, the number of individuals with "severe" disease may be too small for meaningful analysis. An additional limitation is that analysis of a relatively large sample size can yield a highly significant association whose magnitude is unlikely to be clinically meaningful, and this can make

TABLE 2 Mean (unadjusted) absolute anthropometric measurements from first trimester to age 5 years stratified by yes/no asthma outcomes.

	Any asthma admission (1987–2015)		Any asthma medication (2009–2015)		Any inhaled corticosteroid (2009–2015)	
	Yes	No	Yes	No	Yes	No
First-trimester crown–rump length, mm	50.4 (17.2) $n = 1940$	51.9 (16.7) $n = 36,576$	51.5 (16.5) $n = 7393$	51.9 (16.8) $n = 31,123$	51.2 (16.7) $n = 3872$	51.9 (16.7) $n = 34,644$
	0.991 [0.983, 0.998] $p = 0.017$		NS		NS	
Second-trimester femur length, mm	34.2 (10.9) $n = 1736$	33.5 (9.0) $n = 35,708$	34.1 (9.2) $n = 7033$	33.4 (9.0) $n = 30,411$	34.1 (9.5) $n = 3621$	33.5 (9.0) $n = 33,823$
	1.006 [1.001, 1.012] $p = 0.021$		NS		NS	
Second-trimester estimated fetal weight, g	671 (392) $n = 471$	532 (321) $n = 12,947$	567 (345) $n = 2664$	530 (320) $n = 10,754$	590 (356) $n = 1363$	532 (321) $n = 12,055$
	NS		NS		NS	
Mean birth weight (SD), kg	3.30 (0.62) $n = 3472$	3.39 (0.56) $n = 60,451$	3.35 (0.59) $n = 11,798$	3.39 (0.56) $n = 52,125$	3.34 (0.60) $n = 6288$	3.39 (0.56) $n = 57,635$
	0.887 [0.800, 0.982] $p = 0.021$		0.891 [0.841, 0.943] $p < 0.001$		0.907 [0.841, 0.977] $p = 0.011$	
Mean crown heel length (SD), cm	49.5 (2.9) $n = 3423$ $p = 0.032$	49.8 (2.6) $n = 59,868$	49.6 (2.8) $n = 11,672$	49.8 (2.6) $n = 51,619$	49.5 (2.8) $n = 6221$	49.9 (2.6) $n = 57,070$
	NS		0.976 [0.965, 0.988] $p < 0.001$		0.978 [0.964, 0.992] $p = 0.003$	
Mean height at 5 years (SD), cm	112 (12) $n = 436$	113 (10) $n = 13,880$	113 (10) $n = 3108$	113 (9) $n = 11,208$	113 (11) $n = 1545$	113 (10) $n = 12,771$
	0.988 [0.979, 0.996] $p = 0.004$		NS		NS	
Mean weight at 5 years (SD), kg	20.7 (5.3) $n = 340$	20.9 (4.4) $n = 11,925$	20.9 (4.6) $n = 2652$	20.8 (4.4) $n = 9613$	20.9 (4.1) $n = 1229$	20.8 (4.5) $n = 10,966$
	NS		NS		NS	

Note: The p values are from models, which included the following covariates: sex, age/gestation at measurement, offspring age in 2015, maternal age, parity, socioeconomic status, maternal asthma, and maternal smoking. Maternal height was included in analyses, including indices of fetal, neonatal, and childhood length. Maternal weight was included for analyses of fetal, neonatal, or childhood weight. A unique maternal identifier was used to adjust for co-linearity between siblings.

Abbreviations: NS, not significant; SD, standard deviation.

TABLE 3 Coefficients from mixed models which describe the odds ratio for asthma outcomes for changing *z* scores in length between the first trimester, second trimester, birth, and 5 years.

	Odds ratio for outcome (relative to not having the outcome) per change in *z* score size relative to reference					
	Not considering 5-year measurement			Considering 5-year measurement		
	Any asthma admission (1987–2015)	Any asthma medication (2009–2015)	Any inhaled corticosteroid (2009–2015)	Any asthma admission (1987–2015)	Any asthma medication (2009–2015)	Any inhaled corticosteroid (2009–2015)
First-trimester crown–rump length	Reference			Reference		
Second-trimester femur length	1.020 [0.957, 1.087]	1.018 [0.989, 1.047]	1.039 [0.996, 1.083]	1.020 [0.957, 1.088]	1.018 [0.989, 1.047]	1.049 [0.996, 1.083]
Birth length	1.022 [0.965, 1.081]	0.994 [0.968, 1.021]	0.989 [0.950, 1.029]	1.020 [0.964, 1.079]	0.993[0.966, 1.019]	0.987 [0.949, 1.028]
Height at age 5 years	Not included in analysis			0.874 [0.790, 0.967] $p = 0.009$	1.018[0.981, 1.057]	1.002 [0.948, 1.059]

Note: The longitudinal analyses address the fact that within an individual, anthropometric measurements made at different points in time are correlated. The table presents the odds ratio of the outcome associated with a change in the anthropometric measurement relative to the reference (i.e., the first-trimester length). An odds ratio > 1.0 indicates a reduction in *z* score between the earlier gestation and the reference age, which was associated with increased risk for the asthma outcome. The mixed models adjusted for sex, gestation at scan, maternal age, maternal height, parity, socioeconomic status, maternal asthma, and maternal smoking. A unique maternal identifier was used to adjust for co-linearity between siblings.

TABLE 4 Coefficients from mixed models which describe the odds ratio for asthma outcomes for changing *z* scores in weight made in the second trimester, birth, and 5 years.

	Odds ratio for outcome (relative to not having the outcome) per change in *z* score size relative to reference					
	Not considering 5-year measurement			Considering 5-year measurement		
	Any asthma admission (1987–2015)	Any asthma medication (2009–2015)	Any inhaled corticosteroid (2009–2015)	Any asthma admission (1987–2015)	Any asthma medication (2009–2015)	Any inhaled corticosteroid (2009–2015)
Second-trimester estimated fetal weight	Reference			Reference		
Birth weight	1.022 [0.965, 1.081]	0.994 [0.968, 1.021]	0.989 [0.950, 1.029]	0.996 [0.934, 1.063]	0.970 [0.943, 0.988] $p = 0.037$	0.956 [0.916, 0.997] $p = 0.037$
Weight at age 5 years	Not included in analysis			0.944 [0.851, 1.046]	0.970 [0.943, 0.998]	0.999 [0.945, 1.055]

Note: The longitudinal analyses address the fact that within an individual, anthropometric measurements made at different points in time are correlated. The table presents the odds ratio of the outcome associated with a change in the anthropometric measurement relative to the reference (i.e., the second-trimester weight). An odds ratio >1.0 indicates a reduction in *z* score between the earlier gestation and the reference age, which was associated with increased risk for the asthma outcome. The mixed models adjusted for sex, gestation at scan, maternal age, maternal height, parity, socioeconomic status, maternal asthma, and maternal smoking. A unique maternal identifier was used to adjust for co-linearity between siblings.

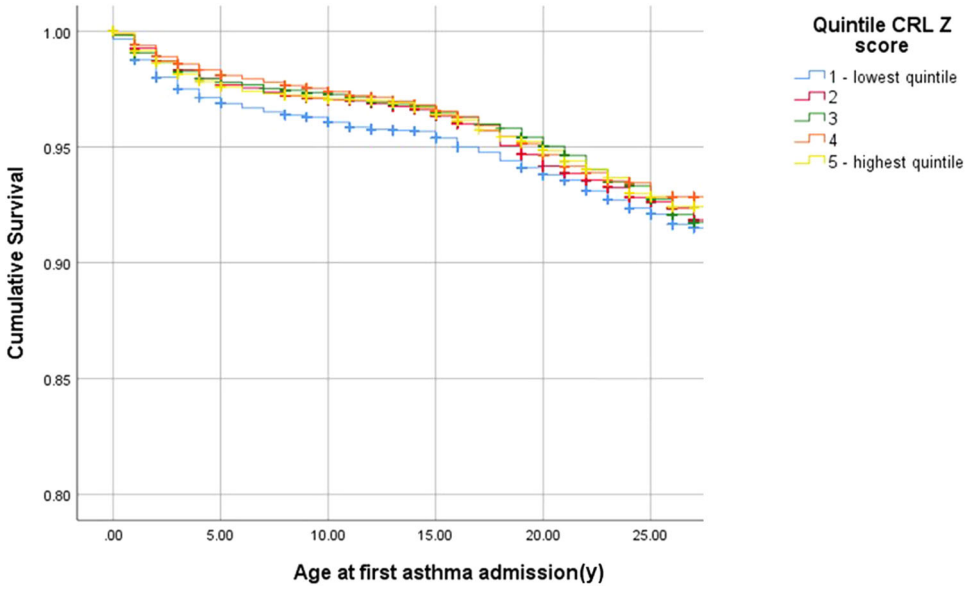

FIGURE 1 A survival curve the age at first asthma admission with stratification by quintile for first-trimester crown–rump length (CRL) *z* score. Log rank analysis $p = 0.024$. In Cox proportional hazards analysis, CRL was associated with age at first admission; relative risk 0.987 per mm CRL [95% CI 0.980, 0.994] $p = 0.001$. [Color figure can be viewed at wileyonlinelibrary.com]

interpretation challenging. A final limitation is that access to data may be limited to a certain time beyond which the data cannot be accessed. Despite these limitations, data linkage offers great potential to researchers and can make a meaningful contribution to our understanding of respiratory conditions.

The median age at first admission was 2 years, and a diagnosis of asthma on admission can be challenging, especially in preschool children. Many cases admitted with "acute asthma" may have had a series of acute lower respiratory tract infections. However, there is no reliable test for asthma, and, as previously discussed studies using routinely acquired data are reliant on the information available.

When single anthropometric measurements were related to asthma outcomes, there were relationships between reduced length at three different gestations/ages and asthma admissions; in the longitudinal analysis, length at 10 weeks and height at 5 years were independently linked to asthma admissions. In contrast, the only association between weight and asthma prescriptions was apparent for birth weight. The more consistent association between length and asthma, relative to weight, maybe at least partly mediated by lung function, which is more closely related to length than weight. The consistency of the association between length and asthma admissions suggests that this is a reliable observation; the association between reduced risk for asthma admission and reduced second trimester length was unexpected. While reduced birth weight has been associated with increased risk for asthma elsewhere,[1,31] the association with receipt of asthma medications should be replicated elsewhere.

Asthma admission and being prescribed asthma medications may lack some precision since there was no standardized methodology for coding admissions and deciding to prescribe asthma medications; this may have weakened any genuine associations. The lack of a robust definition and diagnostic test for asthma may also lead to a lack of precision for the asthma outcomes reported. The median age of the first asthma admission in our data set was 2 years, and this is an age when a diagnosis of asthma is not necessarily secure. Uncertainty of asthma diagnosis also potentially weakens the use of asthma medications as an outcome since a trial of medication does not necessarily equate to an asthma diagnosis.

The present study finding that antenatal SGA was associated with increased risk for asthma is consistent with data from two birth cohorts[11,12] but not the third.[14] Compared to these birth cohorts, the present analysis has a different methodology, includes data from more individuals and with longer follow-ups, but the findings are consistent with two of the three cohorts and therefore add weight to the evidence that antenatal size is related to postnatal asthma outcomes.

The relationship between indices of weight and asthma outcomes was less clear than that for length and outcomes. Although there was no significant association between weight and outcomes when the analysis was restricted to weight in fetal life, at birth, and at 5 years (Table 4), there was an association that approached significance for an increase in weight between the second trimester and birth and reduced odds for being prescribed asthma medications. Also, when the first-trimester length was included as the reference (in the absence of first-trimester weight), increased weight at 5 years was associated with an increased risk for asthma (Supporting Information: Table 6). These results might be due to chance, including an index of length but are also consistent with observations that being SGA at birth[1] and being overweight or obese in childhood are both risk factors for asthma.[32]

The results from this study and others[11,12] raise the possibility that interventions aimed at reducing SGA could reduce asthma risk.

The associations described may not be due to causation but instead may be due to a third factor being causally related to both SGA and asthma. Nonobstetric factors which could be potentially modified and associated with SGA before birth include maternal folic acid intake,[33] smoking[8] and exposure to air pollutants,[9] and nutritional interventions delivered in low and middle-income nations are known to reduce the risk for SGA at birth.[34]

Our analysis included many comparisons and computations, but the possibility of false positive findings was reduced by our applying a p value of <0.025 and also the longitudinal analyses presented in Table 4, which considered data from all gestations/ages. Based on past experience, we created scatter plots to range-check the relationship between gestation and measurement to remove obvious outliers; for example, where gestation was >40 weeks and where cm and mm have apparently been confused. We are not able to return to the original data and clarify anomalous results. While we took this pragmatic approach, an alternative could have been to examine residual plots generated from regression models. We have assumed that missing data were missing at random, but we acknowledge the possibility that missing data have introduced bias. The fact that our results are consistent with studies in other populations reduces the chance of bias in our data affecting the results.

In summary, we have reported how the linkage of routinely acquired data may be a useful approach to respiratory epidemiology, but we also identify the current limitations of this methodology. Our results add to the evidence that antenatal SGA is associated with an increased risk for asthma, and what is now required are interventions designed to reduce the risk for SGA and ultimately reduce childhood asthma.

AUTHOR CONTRIBUTIONS

Lorna Aucott and Steve Turner conceived the study. Anthony Chapman and Steve Turner undertook analysis under supervision of Lorna Aucott. Steve Turner wrote the first draft of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings will be available in Grampian Data Safe Haven at https://www.abdn.ac.uk/iahs/facilities/grampian-data-safe-haven.php#:~:text=The%20Grampian%20Data%20Safe%20Haven%20%28DaSH%29%20is%20a,not%20practicable%20to%20obtain%20consent%20from%20individual%20patients. following an embargo from the date of publication to allow for the commercialization of research findings. The data that supports the findings of this study are available on direct application to each of the data sources. The governance of research use for routinely acquired data means that the authors cannot share data directly.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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