PRETERM BIRTH AND LOW BIRTH WEIGHT CONTINUE TO INCREASE THE RISK OF ASTHMA FROM AGE 7 TO 43

Melanie C Matheson, *Senior Research Fellow*[1], Ana López-Polín D´Olhaberriague, *Research Assistant*[1], John A Burgess, *Research Fellow*[1], Graham G Giles, *Professor*[2], John L Hopper, *Professor*[1], David P Johns, *Associated Professor*[3], Michael J Abramson, *Professor*[4], E Haydn Walters, *Professor*[3], Shyamali C Dharmage, *Professor* [1].

1) Centre for Epidemiology and Biostatistics, The University of Melbourne, Australia;

2) Cancer Epidemiology Centre, Cancer Council Victoria;

3) Menzies Research Institute, University of Tasmania, Australia;

4) Department of Epidemiology & Preventive Medicine, Monash University, Melbourne, Australia

Correspondence to: Dr Melanie C Matheson, Allergy & Lung Health Unit, Centre for Epidemiology & Biostatistics, Melbourne School of Population & Global Health, The University of Melbourne, Victoria 3010 Australia, **T:** +61 3 8344 0734 **M:** 0418 538 427 **E:** mcmat@unimelb.edu.au

ABSTRACT

Background: Perinatal events can influence the development of asthma in childhood but current evidence is contradictory concerning the effects on life-time asthma risk.

Objective: To assess the relationship between birth characteristics and asthma from childhood to adulthood.

Methodology: All available birth records for the Tasmanian Longitudinal Health Study (TAHS) cohort, born in 1961 were obtained from the Tasmanian State Archives and Tasmanian hospitals.

Low birth weight (LBW) was defined as less than 2500 grams. Preterm birth was defined as delivery before 37 weeks gestation. Small for gestational age (SGA) was defined as a birth weight below the 10th percentile for a given gestational age. Multivariate logistic and cox regression were used to examine associations between birth characteristics and lifetime risk of current and incident asthma, adjusting for confounders.

Results: The prevalence of LBW was 5.2%, SGA was 13.8% and preterm was 3.3%. LBW (OR=1.66, 95%CI 1.13,2.44) and preterm birth (OR=1.81, 95%CI 1.00,3.31) were both associated with an increased risk of current asthma between the ages of 7 to 43 years. There was no association between SGA and current asthma risk. However SGA was associated with incident asthma (HR=1.32, 95%CI 1.00, 1.74), and there was an interaction with sex (p-value=0.08), with males having a greater risk of incident asthma (HR=1.70, 95%CI 1.16-2.49) than females (HR=1.04, 95%CI 0.70-1.54).

Conclusions: Preterm birth and LBW were associated with an increased risk of current asthma into middle-age. These findings are the first to demonstrate the continuing impact of these characteristics on asthma risk into middle-age.

Key words

Asthma, Low Birth weight, Prematurity, Small for Gestational Age

Abbreviations:

OR/OR_{Adj}: Odds Ratio/Adjusted Odds Ratio

HR/HR_{Adj}: Hazard Ratio/Adjusted Hazard Ratio

TAHS: Tasmanian Longitudinal Health Study

CI: Confidence Interval

SGA: Small for Gestational Age

AGA: Appropriate for Gestational Age

LBW: Low Birth weight

INTRODUCTION

Evidence that events during fetal life can influence the development of chronic diseases was suggested by Barker et al.[1], who observed an inverse association between birth weight and mortality from chronic obstructive lung disease. Anthropometric parameters at birth, specifically birth weight, reflect fetal growth and, to some extent, nutritional status during pregnancy. He hypothesised that intrauterine conditions causing retarded fetal weight gain might irreversibly constrain the development of the airways and influence maturation of the immune system[1].

Subsequently, many have examined the relationship between birth anthropometric characteristics and asthma risk with inconsistent findings in terms of which of low birth weight (LBW), preterm birth or infant weight gain predispose to risk of asthma. Two recent large reviews and meta-analyses of the association between preterm birth and childhood asthma have been published, demonstrating a consistently increased risk of preschool wheeze[2] and childhood wheezing

disorders[3] in children born preterm. Studies of birth weight have shown inconsistent results with two meta-analyses showing an increased risk of childhood asthma with LBW (<2.5 Kg) [4][5], while another study with some methodological limitations found an increased risk of childhood asthma with higher birth weight[6]. A major limitation of many of these studies was that they did not relate birth weight to gestational age. An infant's size for gestational age, i.e. in-utero growth retardation, may be more important than birth weight per se in the risk of developing asthma in later life. Some infants who are classified as LBW may have birth weights appropriate for gestational age (AGA) while others may be small for gestational age (SGA). The studies on asthma and SGA have been inconclusive, with some studies finding an association[7-9], while others have not[10-12].

There have been relatively few studies that have investigated the long term effects of birth weight on asthma risk into adulthood. A recent meta-analysis reported an increased risk of LBW being associated with asthma into adulthood[5] however the included studies only followed participants into adolescence or early adulthood. Furthermore the majority of studies examining birth anthropometric measurements and asthma risk have been cross-sectional and have therefore been unable to examine if the consistent associations observed between preterm birth and LBW and asthma risk in early life continue into adulthood. We utilised data from the Tasmanian Longitudinal Health Study (TAHS) gathered over a 37 year period to examine the relationship between birth anthropometric measurements, specifically LBW, preterm birth and SGA and the risk of current asthma at different ages and new onset asthma from childhood into middle-age.

METHODS

Tasmanian Longitudinal Health Study (TAHS)

The methods of the baseline study and subsequent follow-up have been published elsewhere [13][14, 15] In brief, TAHS began in 1968 when 8583 Tasmanian children (probands) born in 1961 and attending school in Tasmania were enrolled by their parents who completed a respiratory health questionnaire for the child, who then underwent clinical examination and lung function measurement. Follow-up surveys were completed in 1974, 1979, 1991 and 2002 at the ages of 12, 18, 30 and 43 years respectively. Ethics approval obtained from the Human Research Ethics Committee of the University of Melbourne (HREC Ref. no. 040375.1).

Birth Records Data collection

We obtained all available hospital birth records for children born in 1961 in Tasmania from the Tasmanian State Archive and from Tasmanian hospitals. Birth weight data were available from the state archive for the Queen Alexandra Hospital for Women (Hobart), Beaconsfield District Hospital, Ouse District Hospital, Ulverstone District Hospital, Mersey General Hospital, Toosey Memorial Hospital at Langford and Sheffield District Nursing Centre. Permission to access these records was obtained from the Tasmanian State Archivist. Additional records were obtained from Launceston General Hospital and North West General Hospital. Permission to access these records was obtained from the Human Research Ethics Committee (Tasmania). Information on birth weight was obtained for 2,775 subjects from the original TAHS cohort.

Definitions

LBW was defined according to the WHO definition as a birth weight less than 2,500 grams[16]. **Gestational age** (in weeks) was estimated by subtracting the date of delivery from the expected date of delivery. **Preterm birth** was defined as delivery before the 37th gestational week. **SGA** was defined as a birth weight below the 10th percentile for a given gestational age. To calculate this we transformed of birth data to z scores using the LMS method and against the age- and sex-specific reference standard[17].

Ever asthma was defined by a parent's affirmative response in the 1968 questionnaire to the question: "Has he/she at any time in his/her life suffered from attacks of asthma or wheezy breathing?". The same question was asked in subsequent surveys. In 1968 and 1974 the parents answered on behalf of their children, but in 1991 and 2002 the question was answered by each participant. **Current asthma** at 7, 12, 30 and 43 years was defined by an affirmative response to the Ever Asthma question together with an attack within the previous 12 months. **Age at onset of asthma** was self–reported in the 2002 survey. The participants' responses in the 2002 survey concerning 'asthma ever' and age at onset of asthma were compared with their parent's prospectively gathered responses to the same questions in 1968 and 1974. Where there was disagreement about the participant's early life asthma status or age at onset of asthma, the parent's responses were taken to be correct.

Maternal and paternal smoking in 1968 was reported in the 1968 baseline survey. **Personal smoking** in adulthood was reported by the participant in the 2002 follow-up study. **Paternal occupation** was extracted from the school medical records available for each child. This was

used as a measure of socio-economic status (SES) and coded according to the Australian Standard Classification of Occupations (ASCO) four-digit codes. For paternal occupation these codes were then grouped into 5 major skill groups: (1) Managers/Professionals; (2) Tradespersons and Advanced Clerical; (3) Intermediate clerical and production; (4) Elementary clerical, (5) labourers and related workers. The majority of women were classified as "house duties" and the classifications for maternal occupations were (1) Housewife; (2) Professional; and (3) Tradespersons and other workers.

Statistical Analysis

STATA (Version 13, StataCorp LP, College Station TX, USA) was used to perform the analysis. We used three methods to explore the association between the three exposures (LBW, preterm birth, SGA) and asthma risk over time.

- First, we used multivariate logistic regression to examine the association between the three exposures and current asthma cross-sectionally at 4 time points (age 7, 12, 30, and 43 years).. The potential confounders included in the final models were sex, paternal occupation (measure of SES), maternal smoking and maternal age at the child's birth. The results are presented as odds ratios (OR) with 95% confidence intervals (CI).
- We then accounted for the repeated measures design (given asthma status was recorded 4 time point), by using Generalized Estimating Equations (GEE)[18] and computed an overall estimate of risk of current asthma between age 7 and 43 years.
- Finally a cox regression was also carried out to estimate the association between LBW, preterm birth, SGA and onset of incident asthma up to the age of 43 years. The results are

presented as hazard ratios (HR) with 95% confidence intervals (CI) and were estimated in an adjusted model that also included sex, paternal occupation, maternal smoking and maternal age at the childs birth.

RESULTS

From the original 1968 baseline cohort of 8583, birth weight information was found for 2775 (32.3%) participants. In these birth records 55.3% (n=1534) had information on gestation. A comparison between those with and without a located birth record is shown in Table 1. The two groups did not differ in terms of gender, maternal age at birth of the child, maternal occupation, maternal or paternal allergic disease and maternal smoking. However those with available birth weight data were from slightly lower SES backgrounds (p-value=0.002), were less likely to be from remote areas (p-value=0.0001) and were less likely to have a smoking father.

The mean birth weight and gestational age of the group are reported in Table 2. The mean birth weight was 3.35 kilograms and the mean gestation was 39.9 weeks. Of the 2775 participants in the present study, 5.2% (144) met the criteria for LBW, and for the 1534 also with gestation details 3.3% (51) were preterm and 13.8% (211) were SGA.

LBW, Preterm Birth and SGA and Current Asthma

Table 3 shows the association between LBW, preterm birth, SGA and current asthma at the ages of 7, 12, 30 and 43 years. LBW was associated with an increased risk of current asthma at the ages of 7 (OR=1.75, 95% 1.07-2.87, p-value=0.03), 12 (OR=2.00, 95% 1.03-3.87, p-value=0.04)

and 43 years (OR=1.70, 95% 0.95-3.04, p-value=0.07) but not at age 30 (OR=0.90, 95% 0.33-2.47, p-value=0.84). Furthermore from the GEE analysis there was also a significantly increased risk of current asthma among those with LBW (OR=1.66, 95% CI 1.13,2.44, p-value=0.01). When we additionally adjusted for gestation the results remained the same.

Preterm birth was also associated with a significantly increased risk of current asthma at the ages of 7 (OR=2.40, 95% CI 1.15-4.98, p-value=0.02), 12 (OR=3.24, 95% CI 1.30-8.10, p-value=0.01), but not at 30 or 43 years. The results from the GEE analysis also found an overall increased risk of current asthma associated with preterm birth (OR=1.81, 95%CI 0.99, 3.31, p-value=0.05). No association was observed between small for gestational age and risk of current asthma at the ages of 7, 12, 30 or 43 years. The results from the GEE analysis confirmed the lack of evidence of an association between SGA and risk of current asthma at these ages. We also mutually adjusted the models for SGA and preterm birth for each other and found this made no difference to the associations observed.

LBW, Preterm Birth and SGA and Incident Asthma

The crude incidence of asthma by LBW, preterm birth and SGA is shown in Table 4. The crude incidence of asthma in those with LBW was 14.3/1000/year and 11.0/1000/year in those with normal birth weight (log-rank test for equality p-value=0.10). The crude incidence of asthma was higher in the preterm birth group (16/1000/year) compared to the full term group (11.9/1000/year; log-rank test for equality p-value=0.29). Being SGA was associated with a

higher crude asthma incidence (16.9/1000/year) compared to those AGA (11.3/1000/year; log-rank test for equality p-value=0.006).

We did not observe any association between LBW and preterm birth and incident asthma. SGA was associated with a significantly increased risk of incident asthma (HR=1.32; 95%CI 1.00-1.74, p-value=0.05) and the association remained after additionally adjusting for preterm birth. We explored for any interactions between each birth characteristic and sex on incident asthma. We found a borderline statistically significant interaction between SGA and sex (p-value=0.08). For males the crude incidence of asthma in those with SGA was 25.9/1000/year compared to 12.4/1000/year in those appropriate for gestational age (log-rank test for equality p-value=0.01, Figure 1a Males, b Females). Males with SGA had a significantly greater risk of incident asthma overall (HR=1.70, 95% CI 1.16-2.49, p-value=0.006) than females (HR=1.04, 95% CI 0.70-1.54, p-value=0.86). We did not observe a significant interaction with sex for preterm birth or LBW.

DISCUSSION

We have shown that both LBW and preterm birth are independently associated with the development of current asthma over the life span into middle-age. Our study demonstrated that the impact of LBW and preterm birth has long lasting implications for current asthma risk. We have also shown an increased incidence of asthma associated with being SGA but not with LBW or prematurity. Furthermore this increased risk was only seen in male infants. Our results support the hypothesis that being born preterm or with a LBW may increase asthma susceptibility over the lifespan.

Our results for preterm birth are in line with two recent meta-analyses that have reported a significantly increased risk of asthma in childhood associated with preterm birth. One meta-analysis of over 147,000 children found younger gestational age was associated with childhood asthma up to the age of 10 years [2]. The other meta-analysis of over 1.5 million children from studies with populations born from 1990 onwards also found that preterm birth was associated with wheezing disorders including asthma[3]. An earlier meta-analysis by Jaakkola et al.,[19] that included studies with follow-up of participants into their twenties found that preterm birth was a risk factor for early-onset asthma, but its importance diminished with increasing age. Our study results also showed the increased risk of childhood asthma and provided further evidence that preterm birth continued to increase the risk of asthma well into middle-age. There have been a few individual studies that have looked at the association between preterm birth and risk of asthma into the twenties and early thirties[20-24] but no studies that have looked beyond that into middle-age. Most of these studies reported no association with preterm birth [20-23], with the exception of a recent study by Crump et al.,[24] of over 600,000 Swedish adults (born between 1973 and 1979) that found an increased risk of asthma in the very preterm (23–27 weeks gestation). In our study we had no one with a gestational age before 32 weeks.

We found some evidence of an association between LBW and asthma even after adjustment for weeks of gestation. These findings are consistent with a number of other studies that have followed participants into early adulthood and also found an increased risk of asthma with LBW[25, 26] or reduced risk of asthma with increasing BW[27]. In contrast, there have been

five studies that have not demonstrated any association between LBW and asthma risk into adulthood [21-23, 28, 29]. In our study although we did observe an overall increased risk of current asthma associated with LBW, the association was weakest when participants were aged 30 years. The reason why us and other published studies have found no association around this time of life may be due to the fact that this is the time when maximal lung function has been attained and therefore respiratory symptoms are less pronounced[30].

We found SGA was associated with an increased risk of prevalent asthma only at age 14 but no overall effect across all time points. We also found SGA was associated with incident asthma in males. The reason for this difference is unclear but may reflect that SGA infants are at a greater risk of developing asthma but not necessarily having that asthma persist. Males have a higher rate of asthma in early life and then around puberty this relationship changes and women have a higher prevalence than men. There may be some immunological or structural immaturity in male infants that, combined with being SGA, may lead to a higher incidence of asthma. There is a large amount of evidence on the gender differences in the lungs over the lifespan[31]. Starting in utero, maturation of the airways is more advanced in female than male foetuses in terms of mouth movements which are thought to be critical in determining lung development and in surfactant production[31]. Despite having smaller lungs at birth, female infants are at a lower risk of developing respiratory distress syndrome and transient tachypnoea of the newborn[31]. These factors may make male infants with SGA more likely to develop asthma or wheezy breathing early that may remit.

The mechanisms that may explain the association between these birth characteristics and asthma are not well established. There are several possibilities including that these birth characteristics cause asthma directly. Barker et al.[1], proposed that retarded fetal weight gain may irrecoverably constrain the growth of the airways. Furthermore there is now increasing evidence that babies who have undergone fetal growth restriction and are SGA may have an impaired fetal immune system. A recent study of SGA and AGA infants found infants who were SGA had both decreased FoxP3 expression and decreased suppressive activity of Treg cells[32]. Regulatory T cells (Tregs) play a major role in maintaining self-tolerance, so infants born SGA may have an impaired ability to respond appropriately to allergen stimulation presented after birth[32]. Alternatively, there may be common environmental or genetic factors that increase the likelihood of both these birth characteristics and later life asthma. Maternal smoking during pregnancy and the infant's early-life has been associated with childhood wheezy illness[33] and with an increased risk of delivering a LBW, SGA or a preterm infant[10]. We were unable to examine the interaction with maternal smoking in pregnancy as it was assessed when the children in our study were seven years of age.

The main strength of our study is the length of follow-up from childhood to adulthood. We are the first study to report the association between birth characteristics and asthma risk into middle-age. Another strength of our study is the accuracy of the birth weight data which was collected directly from hospital records. We were limited by the small number of subjects for whom we were able to find information on gestational age. In our study gestational age was determined in some cases by maternal recall of last menstrual period and in other cases by clinical estimate.

Both of these methods have their limitations and are known to overestimate the numbers of preterm and post-term births[34]. However any effect of overestimation of the number of preterm babies is likely to be non-differential in relation to the association with asthma status overtime. Most records were obtained from major facilities in the region which might have produced a bias towards higher SES, but we found no evidence of a systematic bias in records towards those with a higher SES. Also the records may pertain to more difficult or problem pregnancies as these would be referred to the major hospitals in the region. Another limitation was the fact that asthma was assessed by questionnaire data rather than by doctor diagnosis or by measures of lung function and bronchial hyper responsiveness. However, we have previously shown the questions used in this study to be valid against a physician's diagnosis of asthma[35].

In conclusion, our study advances the understanding of the effect of birth characteristics on risk of asthma. Our study is the first to examine risk well into middle-age in a population-based longitudinal cohort and we have demonstrated a consistently increased risk of preterm birth and LBW on risk of current asthma. Recognition of preterm birth as an important risk factor for asthma into middle-age may lead to better monitoring and treatment for susceptible individuals throughout life, which will become increasingly important with more preterm individuals start to enter adulthood and middle-age.

DECLARATION OF INTEREST

MJA has received investigator-initiated grants for unrelated research from Pfizer and Boehringer-Ingelheim, has conducted an unrelated consultancy for AstraZeneca and received

conference attendance assistance from Boehringer-Ingelheim and Sanofi. EHW has given four lectures to general practitioners for unrelated research with honorarium from GSK. None of the other authors declare conflicts of interest with regard to this manuscript.

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CONTRIBUTORS

JLH, DPJ, GGG, MJA, EHW, and SCD conceived the original study and gained funding. ALP, JAB, SCD and MCM developed the analysis plan and conducted data analysis. ALP, JAB, SCD and MCM drafted the manuscript. ALP and CLM were responsible for data collection and management. JAB, MJA, EHW and SCD provided expert advice. ALP, JAB, GGG, JLH, SCD and MCM provided data interpretation. All authors reviewed and refined the manuscript and approved the final version. MCM is guarantor.

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Table 1- Comparison of outcomes and socio demographic factors between those with a birth record identified and those without.

	Birth Record Not Found n/N (%)	Birth Record Found n/N (%)	P value
Individual characteristics			
Females	2,864 / 5,808 (49.3)	1,326/ 2,775 (47.8)	0.19
Maternal Age at childs birth (N, Mean±SD)	N=5,241 33.4±6.1	N=2,733 33.2±6.0	0.16
Rural Area in 1968			
Inner Regional Australia	3,452/5,689 (60.7)	1,553/2,757 (56.3)	
Outer Regional Australia	1,990/5,689 (35.0)	1,182/2,757 (42.9)	
Remote Australia	247 /5,689 (4.3)	22 /2,757 (0.8)	0.0001
Parental characteristics			
Mother smoking	2,027/5,284 (38.4)	1,006/2,753 (36.5)	0.11
Father Smoking	3,207/5,145 (62.3)	1,612/2,694 (59.8)	0.03
Father's Occupation			
(I) Managers/professionals	1,535/5,382 (28.5)	648/2,605 (24.9)	
(II) Tradespersons/Advanced clerical	2,017/5,382 (37.5)	1,048/2,605 (40.2)	
(III) Intermediate clerical/Labourer	1,830/5,382 (34.0)	909/2,605 (34.9)	0.002
Mother's Occupation			
(I) Housewife	4,679/5,094 (91.9)	2,237/2,454 (91.2)	
(II) Professional	199/5,094 (3.9)	91/2,454 (3.7)	
(III) Tradespersons & other	216/5,094 (4.2)	126/2,454 (5.1)	0.20
Paternal Hayfever or/and asthma	1,148/5,134 (22.4)	614 /2,695 (22.8)	0.67
Maternal Hayfever or/and asthma	1,401/5,267 (26.6)	722 /2,752 (26.2)	0.73

Table 2- Birth weight characteristics stratified by sex

Exposures	**Total N**	**Prevalence N (%)**	**95% CI[a]**
Low-Birth weight Infants			
All	2,775	144 (5.2%)	4.3%, 6.0%
Males	1449	55 (3.8%)	2.8%, 4.8%
Females	1326	89 (6.7%)	5.4%, 8.0%
Preterm Infants			
All	1534	51 (3.3%)	2.4%, 4.2%
Males	786	23 (2.9%)	1.7%, 4.1%
Females	748	28 (3.7%)	2.4%, 5.1%
Small for Gestational Age Infants			
All	1534	211 (13.8%)	12.0%, 15.5%
Males	786	90 (11.5%)	9.2%, 13.7%
Females	748	121 (16.2%)	13.5%, 18.8%
Birth weight in kg (mean ± SD)			
All	2775	3.35±0.54	
Males	1449	3.42±0.54	
Females	1326	3.28±0.52	
Gestational weeks (mean ± SD)			
All	1534	39.9±1.50	
Males	786	39.9±1.48	
Females	748	40.0±1.52	

[a] - 95% confidence interval for the prevalence estimate

Table 3- Association between LBW, preterm birth and SGA with current asthma at ages 7, 13, 30 and 43 years of age

			Unadjusted OR (95%CI)	Adjusted OR (95%CI) *	Adjusted OR (95%CI) ‡
	LBW	Normal BW			
Current Asthma	% (n/N)	% (n/N)			
Age 7	8.0% (24/299)	4.9% (120/2461)	1.70 (1.08,2.69) 0.02	1.75 (1.07,2.87) 0.03	1.33 (0.62,2.83) 0.46
Age 12	8.8% (12/136)	4.8% (113/2381)	1.94 (1.04,3.62) 0.04	2.00 (1.03,3.87) 0.04	2.81 (1.09,7.27) 0.03
Age 30	4.6% (5/110)	5.2% (22/425)	0.87 (0.32,2.36) 0.79	0.90 (0.33,2.47) 0.84	1.59 (0.28,9.06) 0.60
Age 43	7.7% (15/194)	5.0% (88/1773)	1.60 (0.91,2.83) 0.10	1.70 (0.95,3.04) 0.07	1.82 (0.77,4.32) 0.17
Age 7-43†	--	--	1.62 (1.12, 2.34) 0.01	1.68 (1.23,2.29) 0.001	1.78 (1.11,2.84) 0.02
Current Asthma	Preterm	At term			
Age 7	6.2% (11/178)	2.9% (39/1347)	2.21 (1.11,4.39) 0.03	2.40 (1.15,4.98) 0.02	2.20 (1.02,4.71) 0.04
Age 12	8.3% (7/85)	2.8% (36/1298)	3.15 (1.36,7.30) 0.008	3.24 (1.30,8.10) 0.01	3.48 (1.38,8.80) 0.008
Age 30	1.6% (1/63)	4.8% (12/249)	0.32 (0.04,2.50) 0.28	0.28 (0.04,2.28) 0.24	0.29 (0.04,2.35) 0.25
Age 43	3.7% (4/109)	2.7% (26/974)	1.39 (0.48,4.06) 0.55	1.31 (0.45,3.87) 0.62	1.41 (0.47,4.17) 0.54
Age 7-43†	--	--	1.83 (1.04,3.22) 0.04	2.05 (1.26, 3.35) 0.004	2.04 (1.23,3.37) 0.006
Current Asthma	SGA	AGA			
Age 7	15.2% (27/178)	13.7% (184/1347)	1.14 (0.74,1.77) 0.55	1.00 (0.61,1.63) 0.99	1.01 (0.62,1.66) 0.96
Age 12	20.0% (17/85)	13.5% (175/1298)	1.60 (0.92,2.78) 0.10	1.76 (0.98,3.16) 0.06	1.79 (1.00,3.23) 0.05
Age 30	9.5%	14.1%	0.64 (0.26,1.61)	0.68 (0.27,1.76)	0.66 (0.26,1.70)

	(6/63)	(35/249)	0.35	0.43	0.39
Age 43	14.7% (16/109)	13.5% (131/974)	1.10 (0.63,1.93) 0.74	1.07 (0.59,1.92) 0.83	1.07 (0.60,1.93) 0.82
Age 7-43†	--	--	1.17 (0.88,1.54) 0.28	1.14 (0.84,1.53) 0.41	1.14 (0.84,1.54) 0.39

* Adjusted for sex, maternal age at child birth, Social Class in 1968, mother smoking in 1968;

† GEE repeated-measures analysis

‡ LBW analysis additionally adjusted for weeks of gestation and the SGA and Preterm analysis are mutually adjusted for each other.

Table 4- Association between incident asthma from birth to age 43 and LBW, Preterm birth And SGA

		Person-years at risk	Incident asthma	Incidence per 1000 person years at risk (95% CI)	HR (95% CI) unadjusted	HR (95% CI) adjusted*	HR (95% CI) adjusted†
LBW	Normal LB	61280.50 3068.50	675 44	11.0(10.2,11.9) 14.3(10.7,19.3)	1.29 (0.95,1.75) 0.10	1.31 (0.95,1.80) 0.10	1.25 (0.78,2.00) 0.36
Preterm	at term preterm	33685.00 873.50	401 14	11.9(10.8,13.1) 16.0(9.49,27.1)	1.33 (0.78,2.25) 0.30	1.44 (0.84,2.46) 0.18	1.46 (0.85,2.49) 0.17
SGA	No Yes	30354.50 4204.00	344 71	11.3(10.2,12.6) 16.9(13.4,21.3)	1.42 (1.10,1.84) 0.007	1.32 (1.00,1.74) 0.05	1.32 (1.00,1.74) 0.05

* Adjusted for sex, maternal age at child birth, social class in 1968, and mother smoking in 1968;

† LBW analysis additionally adjusted for weeks of gestation and the SGA and Preterm analysis are mutually adjusted for each other.

Figure 1: Cumulative probability of asthma by SGA in males (a) and females (b).