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Gestational age at birth and wheezing trajectories at 3–11 years

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ABSTRACT

Objective Children born preterm have an increased risk of asthma in early childhood. We examined whether this persists at 7 and 11 years, and whether wheezing trajectories across childhood are associated with preterm birth.

Design Data were from the UK Millennium Cohort Study, which recruited children at 9 months, with follow-up at 3, 5, 7 and 11 years.

Outcomes Adjusted ORs (aOR) were estimated for recent wheeze and asthma medication use for children born <32, 32–33, 34–36 and 37–38 weeks' gestation, compared with children born at full term (39–41 weeks) at 7 (n=12 198) and 11 years (n=11 690). aORs were also calculated for having 'early-remittent' (wheezing at ages 3 and/or 5 years but not after), 'late' (wheezing at ages 7 and/or 11 years but not before) or 'persistent/relapsing' (wheezing at ages 3 and/or 5 and 7 and/or 11 years) wheeze.

Results Birth <32 weeks, and to a lesser extent at 32–33 weeks, were associated with an increased risk of wheeze and asthma medication use at ages 7 and 11, and all three wheezing trajectories. The aOR for 'persistent/relapsing wheeze' at <32 weeks was 4.30 (95% CI 2.33 to 7.91) and was 2.06 (95% CI 1.16 to 2.69) at 32–33 weeks. Birth at 34–36 weeks was not associated with asthma medication use at 7 or 11, nor late wheeze, but was associated with the other wheezing trajectories. Birth at 37–38 weeks was not associated with wheeze nor asthma medication use.

Conclusions Birth <37 weeks is a risk factor for wheezing characterised as 'early-remittent' or 'persistent/relapsing' wheeze.

INTRODUCTION

Recent research has shown a gradient of adverse health outcomes across the spectrum of gestational age prior to 39 weeks' gestation.^{1,2} Two systematic reviews and meta-analyses have concluded that preterm birth is associated with an increased risk of asthma.^{3,4} Asthma is a chronic inflammatory disorder of the airways, characterised by widespread airflow obstruction that is reversible either with medication or spontaneously.⁵ Three mechanisms have been suggested that link preterm birth and asthma. First, preterm babies are more likely to suffer damage to the lungs or have chronic lung conditions, either due to structural immaturity or as a result of treatment in early life that damaged the lungs.^{3,6} Second, asthma and preterm birth may have common genetic components.³ Third, some prenatal exposures which could induce preterm birth, such as smoking, could also influence the risk of asthma postnatally.³

What is already known on this topic?

- ▶ Birth in gestational age groups <39 weeks tends to be associated with an increased risk of asthma in early childhood (up to 6 years old).
- ▶ By the age of 18 years, it seems that only children born <28 weeks' gestation are at an increased risk of asthma.

What this study adds?

- ▶ To our knowledge, this study is the first to examine the association between gestational age group and wheezing trajectories in children born preterm.
- ▶ Birth <32 weeks and 32–33 weeks is associated with all wheezing trajectories across ages 3–11 years.
- ▶ Birth at 34–36 weeks is associated with early-remittent wheeze and persistent/relapsing wheeze, but not late wheeze.

Existing evidence regarding the impact of preterm birth on asthma as children age is inconsistent, with the apparent effect of gestational age differing depending on the number of years of follow-up.^{3,4} Additionally, studies either focus on the risk of asthma in young children (under 6 years) or adults (over 18 years) born preterm, but very few studies have examined the association between preterm birth and asthma in late childhood and early adolescence.^{7–14} An earlier paper using data from the UK Millennium Cohort Study (MCS) found that children born at <39 weeks' gestation had an increased risk of wheeze and asthma medication use at ages 3 and 5 years.⁸ This present study examines whether being born <39 weeks' gestation is a risk factor for wheeze and asthma medication use in late childhood and early adolescence (7 and 11 years), and explores the association between preterm birth and different trajectories of wheezing from the ages of 3 to 11 years.

METHODS

Millennium Cohort Study

Data were drawn from the MCS, a nationally representative longitudinal study in the UK.¹⁵ Babies born during 2000–2001 were recruited from England, Wales, Northern Ireland and Scotland using a clustered, stratified design. Clusters were by electoral wards, and a baby was eligible if alive at age 9 months, and living in one of the wards.



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Oversampling of certain strata allowed good representation of the four countries, Black and Minority Ethnic populations, and disadvantaged groups. A total of 18 818 children were recruited in the first survey, when caregivers were interviewed about health and sociodemographic characteristics. Follow-up interviews were conducted when the children were 3, 5, 7 and 11 years of age.¹⁵

Assessment of gestational age

Gestational age was calculated using the mother's recall of her gestational due date, which was previously found to have good agreement with hospital records.¹⁶ Gestational age was categorised into very preterm (<32 weeks), moderately preterm (32–33 weeks), late preterm (34–36 weeks), early term (37–38 weeks) and full term (39–41 weeks).

Assessment of asthma/wheeze

Two asthma-related outcome measures were analysed based on questions included in the ages 3–11 year surveys. First, recent wheezing was assessed by maternal interview responses to a validated question^{17 18}: 'Has your child ever had wheezing or whistling in the chest at any time in the past 12 months?' Second, a variable indicating the current use of asthma medications, which was asked at ages 5–11 years, was derived using the response to: 'Is your child taking any medicines on a regular basis prescribed by a doctor, which includes pills, syrups, liquids, inhalers, patches, creams, suppositories or injections?' A child was recorded as taking asthma medications if they were prescribed one or more medications in the following categories (based on British National Formulary codes): bronchodilators like salbutamol and Ventolin, corticosteroids, and cromoglycate and related therapy.¹⁹ Data were not available on frequency or dose.

Inclusion criteria

Singleton children who were present at the age 7 or 11 surveys, with complete information on gestational age at 9 months, and on all asthma/wheezing questions and covariate data at 7 or 11 years were included in the analysis. Children were excluded if their gestational age was improbable given the combinations of birth weight for gestational age centiles, if their natural mother was not the main respondent at the 9-month survey, or if they were born post-term (42+ weeks' gestation), see figure 1.⁸ Additionally, children were excluded if they were coded as taking asthma medication, but had also been recorded as never having asthma, defined as an implausible asthma outcome.

Analysis of asthma-related outcomes at ages 7 and 11 years

Four logistic models were constructed, one for each asthma-related outcome at ages 7 and 11 years. Certain variables were included a priori in the model: child's age at interview, sex, ethnicity and family history of asthma (mother or father has asthma). Additional sociodemographic and pregnancy-related variables were considered as potential confounders. Sociodemographic variables included: household's national statistics socioeconomic classification, area deprivation (index of multiple deprivation), maternal education, maternal age at delivery and lone parent family. Pregnancy-related characteristics included: smoking and alcohol use during pregnancy, duration of breast feeding, birth order and mode of delivery. For details of covariate categories, see table 1.

Each potential confounder was only included in the final model if it was significantly associated with the outcome, once adjusted for the other variables in the model (Wald test $p < 0.05$). For details of variables in final models, see table 2.

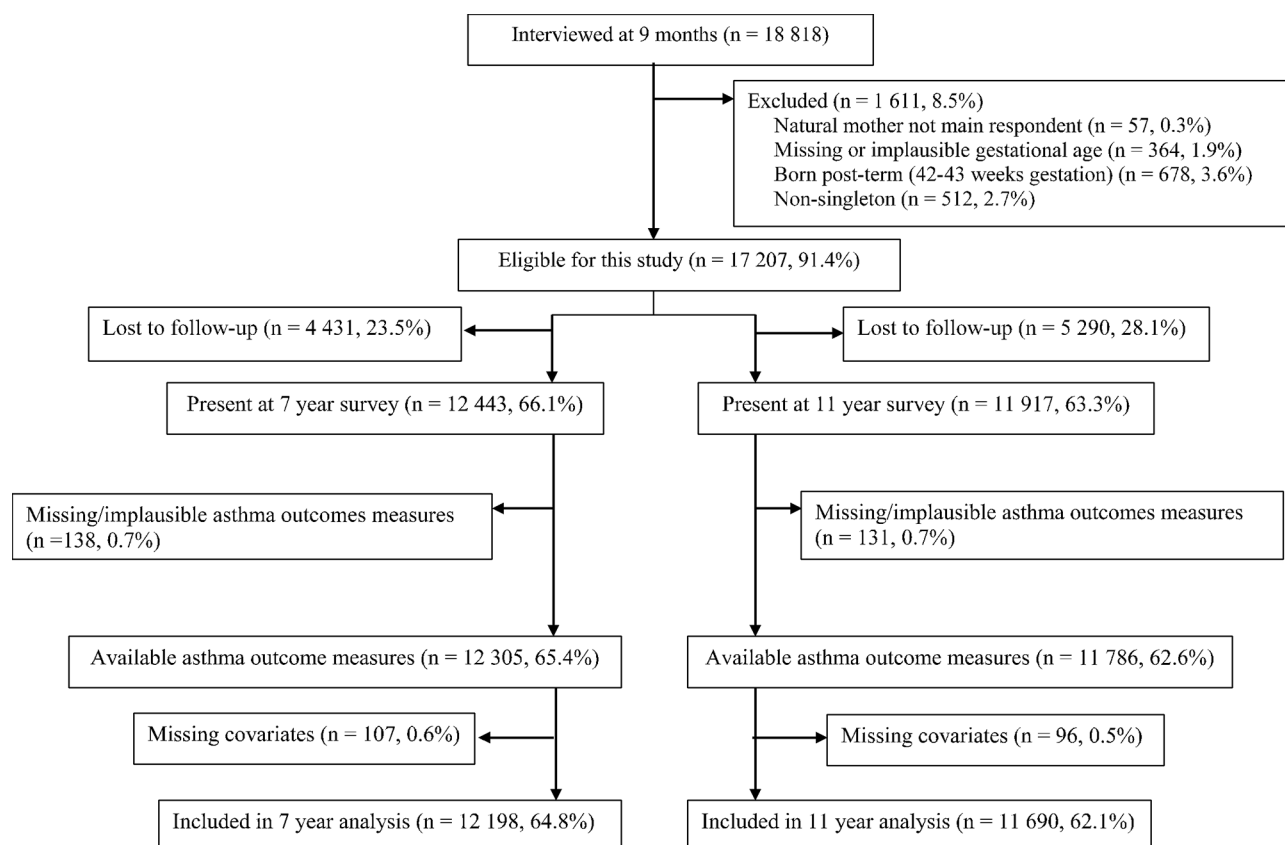


Figure 1 Flow chart of study exclusions and participation. Percentages are of the original sample at 9 months, $n = 18\,818$.

Table 1 Characteristics of Millennium Cohort Study children included in age 11 analysis*

	Total	Gestational age at birth					P value†
		<32 weeks Very preterm	32–33 weeks Moderate preterm	34–36 weeks Late preterm	37–38 weeks Early term	39–41 weeks Full term	
Age 11 analysis	11 690	n=106 (1.0%)	n=106 (0.9%)	n=618 (5.8%)	n=2327 (20.1%)	n=8533 (72.3%)	
Gestational age in weeks, mean (SD)	39.1 (1.9)	28.6 (1.9)	32.7 (0.5)	35.3 (0.7)	37.7 (0.5)	40.0 (0.8)	<0.01
Age at interview, mean (SD)	11.2 (0.3)	11.1 (0.3)	11.1 (0.4)	11.2 (0.3)	11.2 (0.3)	11.2 (0.3)	0.8
Female, n (%)	5807 (48.8)	54 (46.0)	45 (33.9)	288 (46.8)	1118 (47.5)	4302 (49.6)	0.03
Ethnicity, n (%)							
White	9806 (85.3)	81 (79.1)	85 (87.3)	511 (85.2)	1903 (83.1)	7226 (86.0)	0.03
Black and Minority Ethnic groups	1884 (14.7)	25 (20.9)	21 (12.7)	107 (14.8)	424 (16.9)	1307 (14.0)	
Birth weight in grams, mean (SD)‡	3347.1 (572.7)	1226.7 (399.6)	2057.3 (497.9)	2660.2 (490.4)	3166.4 (482.7)	3496.2 (463.9)	<0.01
Household's national statistics socioeconomic classification, n (%)							
Managerial and professional	3471 (26.7)	34 (30.4)	25 (23.2)	171 (25.3)	648 (24.6)	2593 (27.4)	
Intermediate	2480 (21.1)	19 (15.0)	20 (19.5)	139 (21.0)	480 (20.1)	1822 (21.5)	0.3
Routine and manual	4579 (42.5)	45 (46.3)	50 (51.1)	240 (43.4)	960 (45.1)	3824 (41.6)	
Never worked/long-term unemployed	1160 (9.7)	8 (8.4)	11 (6.1)	68 (10.2)	239 (10.3)	834 (9.5)	
Household's area deprivation score, n (%)							
Top quintile	1897 (16.9)	19 (25.7)	13 (21.9)	103 (30.0)	355 (26.5)	1407 (26.1)	
Fourth quintile	1688 (16.8)	20 (24.1)	22 (22.4)	76 (18.2)	343 (19.7)	1227 (20.2)	
Third quintile	2058 (20.0)	13 (10.8)	16 (18.9)	108 (20.3)	415 (20.9)	1506 (19.8)	0.44
Second quintile	2595 (20.0)	21 (21.0)	23 (23.6)	121 (13.5)	517 (17.4)	1913 (16.7)	
Bottom quintile	3452 (26.4)	33 (18.5)	32 (13.2)	210 (18.0)	697 (15.5)	2480 (17.1)	
Maternal education, n (%)§							
Higher (university degree or equivalent)	3811 (28.5)	30 (28.8)	29 (24.2)	182 (24.9)	709 (25.8)	2861 (29.6)	
Medium (A-level or equivalent)	1711 (13.8)	10 (7.7)	11 (10.6)	76 (12.5)	348 (14.0)	1266 (14.0)	
Lower (GCSE or equivalent/overseas)	4608 (42.6)	43 (38.6)	52 (53.1)	269 (44.2)	926 (43.5)	3318 (42.1)	<0.01
No formal qualification	1554 (15.1)	23 (24.9)	14 (12.3)	91 (18.5)	344 (16.7)	1082 (14.2)	
Maternal age at delivery (years) mean (SD)	28.1 (6.0)	27.8 (6.0)	28.6 (6.3)	27.8 (6.0)	28.3 (6.0)	28.1 (6.0)	0.94
Mother lone parent, n (%)	1692 (16.8)	17 (16.3)	15 (13.3)	113 (21.7)	342 (16.6)	1205 (16.6)	0.11
Smoking during pregnancy, n (%)							
Never smoked	7827 (63.2)	67 (63.6)	59 (53.9)	379 (56.7)	1566 (63.0)	5756 (63.9)	
Gave up	1404 (12.8)	13 (9.8)	14 (11.9)	74 (12.4)	257 (12.3)	1046 (13.0)	0.02
Kept smoking	2459 (24.1)	26 (26.6)	33 (34.2)	165 (31.0)	504 (24.8)	1731 (23.1)	
Alcohol use during pregnancy, n (%)							
Never	8187 (69.1)	82 (75.9)	84 (76.3)	451 (70.3)	1696 (72.0)	5874 (68.1)	
Light (1–2 units per week or per occasion)	2702 (23.7)	19 (18.9)	14 (15.8)	126 (21.6)	489 (21.6)	2054 (24.6)	0.1
Moderate to heavy (3 or more units per week or per occasion)	801 (7.2)	5 (5.2)	8 (7.9)	41 (8.1)	142 (6.5)	605 (7.4)	
Duration of breast feeding, n (%)							
Never breast fed	3596 (34.8)	33 (33.4)	33 (35.1)	222 (42.9)	765 (37.0)	2543 (33.5)	
<1 month	2287 (17.8)	15 (16.2)	21 (18.0)	126 (17.3)	473 (17.9)	1652 (17.7)	
1–3 months	2036 (16.9)	33 (29.6)	27 (24.0)	122 (18.0)	411 (17.9)	1443 (16.3)	<0.01
4+ months	3771 (30.6)	25 (20.9)	25 (22.9)	148 (21.9)	678 (27.2)	2895 (32.5)	
Birth order, n (%)							
First born	4896 (41.9)	52 (50.4)	48 (46.7)	272 (41.4)	855 (38.1)	3669 (42.8)	0.01
Type of delivery, n (%)¶							
Normal	8050 (70.6)	40 (41.8)	46 (41.5)	351 (58.0)	1422 (62.5)	6191 (74.6)	
Assisted	1139 (9.4)	5 (3.8)	5 (4.6)	47 (8.8)	142 (5.8)	940 (10.6)	<0.01
Caesarean	2480 (20.0)	60 (54.4)	55 (55.0)	220 (33.3)	760 (31.7)	1385 (14.8)	
Family history of asthma, n (%)	2921 (26.3)	22 (24.6)	34 (34.2)	162 (25.2)	560 (25.0)	2143 (26.6)	0.41

Unweighted counts and survey-weighted proportions reported.

*Similar demographics at age 7 analysis, not included.

†From weighted test for association.

‡Ten birth weight data missing.

§Six maternal qualification data missing.

¶Twenty one type of delivery data missing.

GCSE, General Certificate of Secondary Education.

Analysis of wheezing trajectories

MCS children who satisfied the previous inclusion criteria, but additionally were present at the age 3, 5, 7 and 11 surveys were included (n=9918). Children were classified into recognised

wheezing trajectories according to their wheezing trajectory at ages 3–11: 'no wheeze' (no wheeze present at ages 3, 5, 7 and 11 years); 'early-remittent wheeze' (wheezing at 3 and/or 5 years but not thereafter); 'late-wheeze' (wheezing at 7 and/or 11 years

Table 2 Asthma outcomes by gestational age group at ages 7 and 11

	Gestational age groups				
	<32 weeks; very preterm	32–33 weeks; moderate preterm	34–36 weeks; late preterm	37–38 weeks; early term	39–41 weeks; full term
Wheezing in the last 12 months					
At 7 years	n=103	n=110	n=629	n=2417	n=8939
n (%)	25 (22.2)	23 (20.6)	79 (13.7)	304 (12.3)	1033 (11.4)
OR unadjusted (95% CI)	2.22 (1.26 to 3.90)	2.01 (1.18 to 3.41)	1.23 (0.90 to 1.67)	1.09 (0.94 to 1.26)	1
Fully adjusted OR (95% CI)*	2.04 (1.12 to 3.72)	1.85 (1.11 to 3.10)	1.19 (0.86 to 1.64)	1.06 (0.92 to 1.23)	1
At 11 years	n=106	n=106	n=618	n=2327	n=8533
n (%)	22 (17.1)	21 (20.5)	78 (12.5)	283 (11.5)	976 (11.1)
OR unadjusted (95% CI)	1.65 (0.96 to 2.82)	2.06 (1.13 to 3.76)	1.14 (0.82 to 1.58)	1.04 (0.87 to 1.23)	1
Fully adjusted OR (95% CI)*	1.64 (0.93 to 2.91)	1.84 (1.04 to 3.25)	1.12 (0.81 to 1.54)	1.03 (0.87 to 1.22)	1
Currently on asthma medication					
At 7 years	n=103	n=110	n=629	n=2417	n=8939
n (%)	10 (12.8)	8 (7.8)	40 (5.8)	127 (5.4)	389 (4.3)
OR unadjusted (95% CI)	3.29 (1.45 to 7.44)	1.90 (0.88 to 4.16)	1.38 (0.95 to 2.00)	1.27 (1.02 to 1.58)	1
Fully adjusted OR (95% CI)*	3.01 (1.25 to 7.28)	1.71 (0.82 to 3.55)	1.35 (0.92 to 1.97)	1.24 (0.99 to 1.56)	1
At 11 years	n=106	n=106	n=618	n=2327	n=8533
n (%)	11 (12.4)	13 (14.5)	39 (5.0)	134 (5.5)	425 (4.9)
OR unadjusted (95% CI)	2.75 (1.28 to 5.91)	3.29 (1.60 to 6.80)	1.03 (0.71 to 1.50)	1.13 (0.90 to 1.41)	1
Fully adjusted OR (95% CI)*	2.73 (1.24 to 6.02)	2.96 (1.48 to 5.91)	1.00 (0.69 to 1.47)	1.12 (0.89 to 1.41)	1

Unweighted counts and survey-weighted proportions reported.

*Adjusted for child's sex, ethnicity and age at interview; household's national statistics socioeconomic classification, maternal age at delivery, lone parent family and alcohol use during pregnancy.

but not before); and 'persistent/relapsing wheeze' (wheezing at ages 3 and/or 5 and again at 7 and/or 11 years).^{20–22} ORs for each wheezing trajectory by gestational age group were calculated using multinomial logistic regression with adjustment for the same covariates as the previous logistic models. Children with 'no wheeze' at all surveys were the comparison group.

All analyses were conducted in Stata V.13 using survey weights to account for the study design, oversampling at recruitment and attrition bias between surveys.²³ The survey weights for attrition took into account many sociodemographic characteristics collected at the first survey.²³

The MCS initial survey, all follow-up surveys and secondary data analyses were granted ethical approval from the multi-centre research ethics committee.

RESULTS

At both the age 7 and 11 years survey, 98.1% of present children had complete information on asthma-related outcomes and covariates (n=12 198 and 11 690 at the age 7 and 11 surveys, respectively). Approximately 7.7% of children at both surveys were born <37 weeks' gestation. Increasing prematurity was associated with decreasing birth weight (table 1). Black and Minority Ethnic group babies were over-represented in the lower gestational age groups. Gestational age was also significantly associated with sex, maternal qualifications, smoking during pregnancy, duration of breast feeding, birth order and type of delivery.

At ages 7 and 11, approximately 11% of children had recent wheeze and 5% were currently on asthma medication (table 2). Among the 9918 children with asthma-related data available at 3, 5, 7 and 11 years, 15.8% were classified as 'early-remittent wheeze', 6.7% as 'late wheeze', 11.4% as 'persistent/relapsing wheeze' and 65.8% as 'no wheeze'.

Children born at <32 weeks' gestation were at an increased risk of asthma-related outcomes at ages 7 and 11: they had a threefold increased odds for current use of asthma

medication and a twofold increased odds for recent wheeze at both ages (table 2). They also had three to four times the odds for all wheezing trajectories compared with their full-term peers (table 3). Children born at 32–33 weeks' gestation also tended to be at an increased risk of both asthma-related outcomes, but these effects were not as large and were not always statistically significant. They also had an increased odds for all wheezing trajectories compared with their peers born at full term, but this was only statistically significant for 'persistent/relapsing' wheeze (OR 2.06, 95% CI 1.16 to 2.69). There were no statistically significant associations between birth at 34–36 weeks' gestation and wheezing in the last 12 months or current asthma medication use at age 7 or 11. While these children had approximately 1.4 times the odds of 'early-remittent' and 'persistent/relapsing' wheeze compared with those born at full term, they were at no increased risk of 'late' wheeze. There were no statistically significant associations between birth at 37–38 weeks' gestation and either of the asthma-related outcomes at age 7 or 11 years, nor any of the wheezing trajectories.

A comparison of the results of this analysis at ages 7 and 11, with that of a previous study that examined asthma outcomes in the MCS at ages 3 and 5, can be found in figure 2.⁸

DISCUSSION

Our study suggests that children born preterm (<37 weeks' gestation) are at an increased risk of 'early-remittent' and 'persistent/relapsing' wheeze, and there is a gradient of risk observed across the gestational age groups. Children born at <32 weeks, and to a lesser extent, those born at 32–33 weeks, are also more likely to experience 'late' wheeze than those born at full term. The results of the analysis for recent wheeze and asthma medication use at ages 7 and 11 are concordant with the findings regarding wheezing trajectory. Children <32 weeks and to a lesser extent those born at 32–33 weeks were at an increased risk for these outcomes. A previous analysis of the same cohort identified these groups

Table 3 OR for different wheezing trajectories (early-remittent wheeze, late wheeze and persistent/relapsing wheeze) by gestational age group

Asthma trajectories	Gestational age groups				
	<32 weeks; very preterm	32–33 weeks; moderate preterm	34–36 weeks; late preterm	37–38 weeks; early term	39–41 weeks; full term
No wheeze (no wheezing at 3, 5, 7 and 11)	n=50 (41.3%)	n=58 (55.4%)	n=349 (61.0%)	n=1317 (66.1%)	n=4784 (67.4%)
Early-remittent wheeze (only wheeze at 3 and/or 5)	n=27 (25.2%)	n=24 (19.1%)	n=119 (19.4%)	n=324 (16.7%)	n=1072 (15.5%)
Relative risk ratio (95% CI)*	2.72 (1.49 to 4.96)	1.52 (0.89 to 2.60)	1.38 (1.10 to 1.74)	1.11 (0.94 to 1.29)	1
Late wheeze (only wheeze at 7 and/or 11)	n=13 (8.7%)	n=11 (7.9%)	n=26 (5.7%)	n=135 (5.6%)	n=481 (6.8%)
Relative risk ratio (95% CI)*	2.19 (1.04 to 4.62)	1.42 (0.71 to 2.86)	0.91 (0.58 to 1.42)	0.85 (0.66 to 1.09)	1
Persistent/relapsing wheeze (wheeze in early life at ages 3 and/or 5, and later in life at ages 7 and/or 11)	n=29 (24.8%)	n=19 (17.6%)	n=80 (13.9%)	n=239 (11.6%)	n=761 (10.3%)
Relative risk ratio (95% CI)*	4.30 (2.33 to 7.91)	2.06 (1.16 to 2.69)	1.45 (1.09 to 1.94)	1.15 (0.97 to 1.38)	1

Unweighted counts and survey-weighted proportions reported.

*Adjusted for child's sex, ethnicity and age at interview; family history of asthma, household's national statistics socioeconomic classification, maternal age at delivery, lone parent family and alcohol use during pregnancy.

as being at an increased risk of the same outcomes at ages 3 and 5 years.⁸ In contrast, children born at 34–36 weeks were not at a statistically significant increased risk of wheeze nor asthma medication use at 7 and 11, despite previously being at an increased risk of asthma at ages 3 and 5 years.⁸ Birth at 37–38 weeks' gestation appears not to be associated with these adverse outcome measures at the ages of 7 and 11, or any of the wheezing trajectories.

The association between preterm birth and wheeze in this study may suggest that the children experienced damage to the lungs (either mechanical or because they were not yet fully developed), as genetic (family history of asthma) and prenatal and postnatal exposures (such as smoking and social deprivation) were considered in the regression models. Other studies have reported an increased risk of asthma after mechanical ventilation in those born preterm and low birth weight.^{11 24 25} While

the aetiology is unclear, persistent-relapsing wheeze may point to early, and long-lasting, damage to the lung tissue resulting in wheezing throughout childhood. Early-remittent wheeze, however, may include wheezing due to higher rates of respiratory infection or more transient lung injury. Preterm babies are also at increased risk of respiratory tract infections, an effect that can persist into early childhood.²⁶ This may explain the higher risk of wheezing in early childhood, seen in Boyle's age 3 and 5 results,⁸ and in our findings that decreasing gestational age is associated with increasing risk of 'early-remittent' wheeze. Late wheeze, likewise, may not represent true asthma, but rather an infective episode.

This increase in 'early-remittent' wheeze in children born preterm may also help explain some of the conflicting published evidence: a meta-analysis comparing under 5 years with over 5 years reports that preterm birth is associated with wheezing in

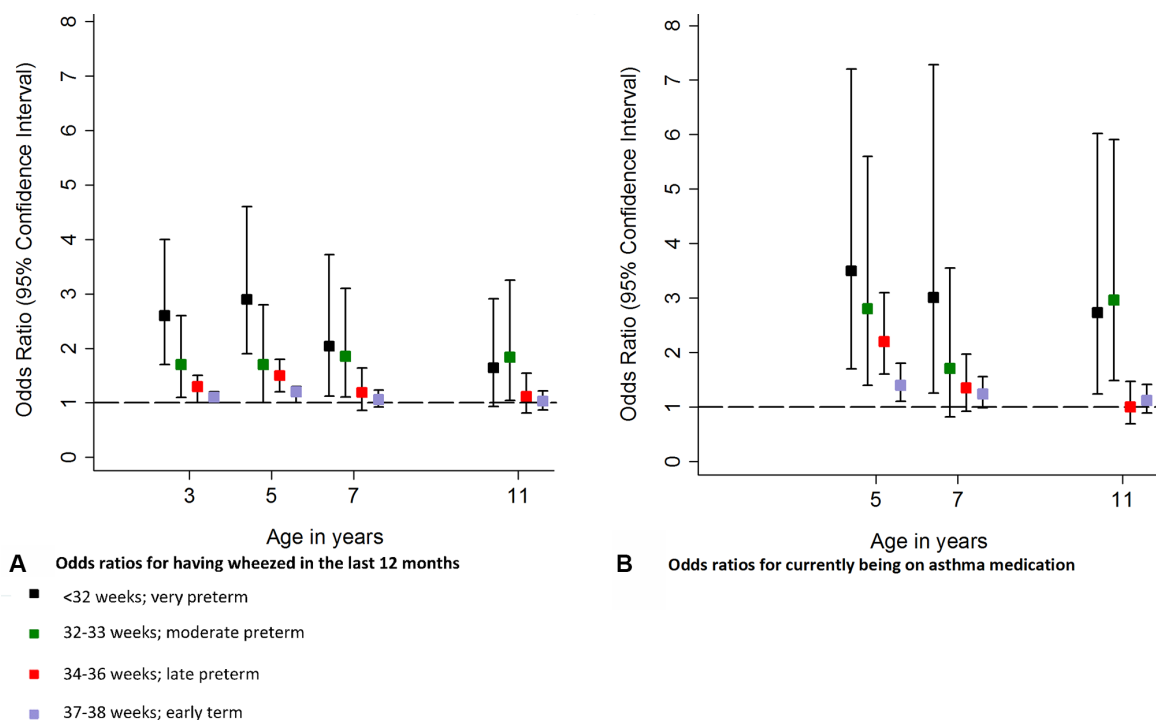


Figure 2 ORs for having wheezed in the last 12 months (A), and for currently being on asthma medication (B) at ages 3, 5, 7, and 11 years by gestational age group. ORs presented at 3 and 5 are from Boyle *et al*,⁸ adjusted for: child's age at interview, sex and ethnicity; maternal age at delivery, marital status education and occupation; whether the child was mother's first-born; whether child was ever breast fed; and smoking and drinking during pregnancy.

both age groups,⁴ and other studies in young children that tend to find a statistically significant association between gestation <39 weeks and asthma in children <6 years.^{7–9} However, another meta-analysis comparing children under and over 10 years finds that the impact of prematurity on asthma disappears with age.³ In addition, the latter meta-analysis included older studies, and studies with older children. This highlights the importance of considering the changing pattern of wheeze through childhood, and the need for a standard definition of paediatric wheezing trajectories.

It will be important to follow the longer term prognosis for the preterm children in the MCS. Another UK cohort study (Avon Longitudinal Study of Parents and Children) followed 12 303 children born in the early 1990s from birth to age 16.5 years, and found birth <37 weeks to be associated with a higher risk of preschool-onset and mid-childhood-onset remitting, and continuous wheeze into mid-teens.²⁷ Studies that examine cohorts of adults (18+ years) tend not to find a statistically significant association unless participants are born extremely preterm (<28 weeks' gestation).^{12–14} However, the evidence of no effect of preterm birth on asthma in adults comes mostly from Scandinavia and Finland, with cohorts born in the 1970s, and therefore, these results may not be applicable to our study population.

Strengths and limitations

Preterm births less than 34 weeks are relatively rare, and only comprised 2% of the MCS population at age 11. As a consequence, our analysis was limited by relatively small numbers in these groups, and thus p values should be interpreted with caution. For example, there is no statistically significant association for reported wheeze at age 11 in those <32 weeks, yet other results from this study would indicate they are still at increased risk of respiratory symptoms at this age. Additionally, our analysis is limited due to parental report of gestational age, and recent wheeze and asthma medication use. These outcome measures may be affected by recall bias, as parents of preterm children may be more likely to report their child wheezing. Finally, while our results suggest that 'persistent/relapsing' wheeze may be related to damage to the lung tissue, no data were available to investigate this association, for example, use of mechanical ventilation.

However, our study has a number of strengths. First, it is a large, nationally representative cohort providing findings that are generalisable to the UK and similar settings. Second, data were available for a large number of potential confounders. Finally, owing to the availability of longitudinal data, we were able to examine wheezing trajectories of preterm children across the spectrum of gestational age at birth; to our knowledge, this is the first study to do so.

Our findings are strengthened by the use of a validated measure of wheeze, together with parental report of asthma medication. Use of asthma medications tends to be a reflection of access to healthcare, management by clinicians and carers, and severity of the condition. In the MCS, as children have access to the UK's universal healthcare system, it is likely that asthma medication is a meaningful measure of disease severity. Future studies should examine the outcome of asthma medications use by type and frequency.

CONCLUSION

Children born preterm (<37 weeks' gestation) tend to be at an increased risk of both 'early-remittent' wheeze and 'persistent/relapsing' wheeze compared with their full-term peers, and

our results suggest a gradient of risk across the gestational age groups. Future research should examine which factors predict the different wheezing trajectories in preterm children, which may help elucidate the underlying mechanisms. Additionally, further follow-up of the MCS and other birth cohorts will allow researchers to determine whether preterm children at risk of 'persistent/relapsing wheeze' from ages 3 to 11 continue to have asthma-related symptoms as they enter adulthood. Identifying modifiable risk factors for 'persistent/relapsing' wheeze should be a priority, in order to reduce and manage the long-term respiratory morbidity caused by preterm birth.

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Data sharing statement All data are freely available from the Millennium Cohort Study.

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REFERENCES

- 1 Baron IS, Litman FR, Ahronovich MD, *et al.* Late preterm birth: a review of medical and neuropsychological childhood outcomes. *Neuropsychol Rev* 2012;22:438–50.
- 2 Blencowe H, Cousens S, Chou D, *et al.* Born too soon: the global epidemiology of 15 million preterm births. *Reprod Health* 2013;10(Suppl 1):S2.
- 3 Jaakkola JJ, Ahmed P, Ieromimon A, *et al.* Preterm delivery and asthma: a systematic review and meta-analysis. *J Allergy Clin Immunol* 2006;118:823–30.
- 4 Been JV, Lugtberg MJ, Smets E, *et al.* Preterm birth and childhood wheezing disorders: a systematic review and meta-analysis. *PLoS Med* 2014;11:e1001596.
- 5 Asher I, Pearce N. Global burden of asthma among children. *Int J Tuberc Lung Dis* 2014;18:1269–78.
- 6 Baraldi E, Filippone M. Chronic lung disease after premature birth. *N Engl J Med* 2007;357:1946–55.
- 7 Goyal NK, Fiks AG, Lorch SA. Association of late-preterm birth with asthma in young children: practice-based study. *Pediatrics* 2011;128:e830–e8.
- 8 Boyle EM, Poulsen G, Field DJ, *et al.* Effects of gestational age at birth on health outcomes at 3 and 5 years of age: population based cohort study. *BMJ* 2012;344:e896–e909.
- 9 Dik N, Tate RB, Manfreda J, *et al.* Risk of physician-diagnosed asthma in the first 6 years of life. *Chest* 2004;126:1147–53.
- 10 Gessner BD, Chimonas MA. Asthma is associated with preterm birth but not with small for gestational age status among a population-based cohort of Medicaid-enrolled children <10 years of age. *Thorax* 2007;62:231–6.
- 11 Källén B, Finnström O, Nygren KG, *et al.* Association between preterm birth and intrauterine growth retardation and child asthma. *Eur Respir J* 2013;41:671–6.
- 12 Crump C, Winkleby MA, Sundquist J, *et al.* Risk of asthma in young adults who were born preterm: a Swedish national cohort study. *Pediatrics* 2011;127:e913–e20.
- 13 Bråbäck L, Hedberg A. Perinatal risk factors for atopic disease in conscripts. *Clin Exp Allergy* 1998;28:936–42.
- 14 Steffensen FH, Sørensen HT, Gillman MW, *et al.* Low birth weight and preterm delivery as risk factors for asthma and atopic dermatitis in young adult males. *Epidemiology* 2000;11:185–8.
- 15 Hansen K. *Millennium Cohort Study first, second, third, fourth, and fifth Surveys: a guide to the datasets.* London: Centre for Longitudinal Studies, Institute of Education, University of London, 2014.
- 16 Poulsen G, Kurinczuk JJ, Wolke D, *et al.* Accurate reporting of expected delivery date by mothers 9 months after birth. *J Clin Epidemiol* 2011;64:1444–50.

- 17 Asher MI, Keil U, Anderson HR, *et al.* International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. *Eur Respir J* 1995;8:483–91.
- 18 Asher M, Stewart A. Worldwide variations in the prevalence of asthma symptoms: the International Study of Asthma and Allergies in Childhood (ISAAC). *Eur Respir J* 1998;12:315–35.
- 19 Carson C, Sacker A, Kelly Y, *et al.* Asthma in children born after infertility treatment: findings from the UK Millennium Cohort Study. *Hum Reprod* 2013;28:471–9.
- 20 Stein RT, Martinez FD. Wheezing trajectories in childhood: lessons from an epidemiological approach. *Paediatr Respir Rev* 2004;5:155–61.
- 21 Taylor-Robinson DC, Pearce A, Whitehead M, *et al.* Social inequalities in wheezing in children: findings from the UK Millennium Cohort Study. *Eur Respir J* 2016;47:818–28.
- 22 Sears MR, Greene JM, Willan AR, *et al.* A longitudinal, population-based, cohort study of childhood asthma followed to adulthood. *N Engl J Med* 2003;349:1414–22.
- 23 Mostafa T. *Millennium cohort study: technical report on response in sweep 5 (age 11)*: Centre of Longitudinal Studies, Institute of Education, 2014.
- 24 Mai XM, Gädölin PO, Nilsson L, *et al.* Asthma, lung function and allergy in 12-year-old children with very low birth weight: a prospective study. *Pediatr Allergy Immunol* 2003;14:184–92.
- 25 von Mutius E. Progression of allergy and asthma through childhood to adolescence. *Thorax* 1996;51(Suppl 1):S3–S6.
- 26 Panico L, Stuart B, Bartley M, *et al.* Asthma trajectories in early childhood: identifying modifiable factors. *PLoS One* 2014;9:e111922.
- 27 Granell R, Henderson AJ, Sterne JA. Associations of wheezing phenotypes with late asthma outcomes in the Avon Longitudinal Study of Parents and Children: A population-based birth cohort. *J Allergy Clin Immunol* 2016;138.