Comparison of the Associations of Early Life Factors on Wheezing-Phenotypes in Preterm-Born Children and Term-Born Children

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This work was funded as follows: SJK reports support from Nutricia Research Foundation for performing this study. SK reports funding from Medical Research Council (MR/M022552/1) for this submitted work; and grants from National Institute for Health Research (16/111/106), Welsh Government, and European Commission FP7 outside of this submitted work.

Conflict of interest: None declared.

Running Head: Wheezing Phenotypes in Preterm-born Children

Abbreviations list

IUGR	intrauterine growth restriction
MCS	Millennium Cohort Study
OR	odds ratio

Abstract

Although respiratory symptoms, including wheezing, are common in preterm-born subjects, the natural history of the wheezing-phenotypes and the influence of early life factors and characteristics on phenotypes are unclear. Participants from the Millennium Cohort Study born between 2000-2002 were studied at 9 months, 3, 5, 7, and 11 years. We used data-driven methods to define wheezing-phenotypes in preterm-born children and investigated if the association of early life factors and characteristics on wheezing-phenotypes were similar between preterm- and term-born children. 1,049/1502 (70%) preterm-born children, and 12,307/17,063 (72%) term-born had recent wheeze data for three or four time-points. Recent-wheeze was greater at all time-points in preterm-born than term-born group. Four wheezing-phenotypes were defined: no/infrequent, early, persistent and late for both groups. Early life factors and characteristics, especially antenatal smoking, atopy, male gender, were associated with increased rates for all phenotypes in both groups breast feeding was protective in both groups, except late-wheeze in the preterm group. Preterm-born children had similar phenotypes to term-born children. Although early life factors and characteristics were similarly associated with the wheezing-phenotypes in both groups, the preterm group had higher rates of early and persistent-wheeze. However, a large proportion of preterm-born children had early-wheeze which resolved with time.

KEYWORDS

Millenium Cohort Study, Prematurity, Wheeze,

Introduction

Due to increased respiratory symptoms and lower attainment of peak lung function in preterm-born children, there have been concerns that they may be at risk of premature development of chronic obstructive pulmonary disease.(1) Whilst it has been established that very preterm-born children born at <32 weeks' gestation have longer term lung function deficits,(2) especially if they develop bronchopulmonary dysplasia in infancy (also called chronic lung disease of prematurity,(3) it is increasingly recognised that even those born late preterm (33-36 weeks' gestation) have lung function deficits.(4, 5) Two recent longitudinal studies have reported that lung function declines with age. (6, 7) Doyle et al. reported the longitudinal outcomes at 8 and 18 years of life of infants born at <28 weeks' gestation or <1,000g in a cohort born after surfactant was introduced. Deficits in lung function increased between the two time points compared to term controls.(6) Simpson et al. studied children born at ≤32 weeks gestation in early and mid-childhood; and again reported declines in lung function between the two time points compared to term controls.(7) Respiratory symptoms are also increased showing a gradient of increasing wheeze with increasing prematurity.(8, 9) Even those born early term (37-38 weeks' gestation) have greater respiratory symptoms than children born at 39-40 weeks' gestation.(10, 11)

In asthma, a complex heterogeneous disease, a number of wheezing-phenotypes have been described based on wheezing patterns over time.(12-15) It is important to accurately define wheezing-phenotypes as some, such as persistent-wheeze, are associated with longer term decrements in lung function; furthermore different underlying mechanisms or endotypes may be associated with the different wheezing-phenotypes.(12, 14, 16, 17) After preterm-birth, it has been assumed that long-term respiratory outcomes are the consequence of dysregulated lung growth(18, 19) and neonatal treatment with early wheezing in infancy persisting into adulthood without ever reaching optimal lung function.(1) Simpson et al. studied respiratory symptoms from early to mid-childhood and symptoms remained consistent.(7) However, thus far, no longitudinal studies have reported the wheezing phenotypes in preterm-born children. Wheezing-phenotype studies have included preterm-born children in their cohorts but have not specifically examined them.(13, 14, 20) In addition, the association of early life factors and characteristics with wheezing-phenotypes in preterm-born children is unclear. We postulated that preterm-born children will differ from term-born children because they are born at an earlier stage of lung development and may have greater noxious exposures in early life e.g. to supplemental oxygen, mechanical ventilation, and neonatal infections amongst others compared to term-born children. Wheezing illnesses are heterogeneous in early childhood and only some are associated with asthma in later life. Therefore, asthma and wheezing cannot be segregated. Whilst we know some of the long-term consequences of preterm birth, there may be other endotypes that are important in the development of wheezing illnesses in this population. It is important to determine these associations as it could potentially lead to the identification of preterm-born children at risk of the different wheezing-phenotypes. If any early life factor and characteristics is modifiable then long term respiratory symptoms may be modifiable. Therefore, using a well-established cohort, we, (a) defined the different wheezing-phenotypes in preterm-born children comparing results with term-born children; and (b) identified and compared the association between early life factors and characteristics and the different wheezing-phenotypes in the term- and preterm-born groups separately.

METHODS

Millennium Cohort Study (MCS)

MCS is a cohort of 19,517 children born in the United Kingdom between 2000 and 2002 as previously described.(21, 22) The data for all MCS sweeps is available from the UK Data Service to download.(23) All data were collected at face-to-face interviews as described in web appendix 1. At nine months of age, data were collected on pregnancy, birth and early life factors, characteristics and on respiratory symptoms (including "wheeze-ever" and "recent-wheeze" – defined as parental reporting of wheezing or whistling in the chest in the last 12 months) at 3, 5, 7 and 11 years of age. Recruitment, ethical approval and parental consent were obtained as described previously.(24)

Statistical analyses

Preterm- and term-born were defined as birth at <37 and ≥37 weeks' gestation respectively. Birth-weight z-scores were calculated using the LMS Growth program (Medical Research Council, United Kingdom) correcting for gestation and gender.(25) Intrauterine growth restriction (IUGR) was defined as <10th centile for birth-weight corrected for gender and gestation. (26),(27) Demographics and wheezing symptoms were compared between preterm and term groups using independent sample T-tests or chi squared tests.

Wheezing-phenotypes were derived from respiratory symptoms reported on at least three occasions. LatentGOLD (Statistical Innovations, Boston, Ma., United States America) was used to estimate latent class cluster models by data driven methods as described in web appendix 1. The class posterior probability was used to assign each wheezing pattern to the class of wheezing-phenotype which had the highest probability of belonging to, using the probabilities specified by the LatentGOLD analysis. Demographics for the different wheezing-phenotypes were compared using Analysis of variance (ANOVA) or Chi squared tests. Using cases with complete data for the early life factors and characteristics for both the preterm group and the term group, we conducted a multi-nomial logistic regression with wheezing-phenotype as the outcome variable using the no/infrequent wheeze class as the reference group. Early life factors and characteristics which have been reported to have a direct association on preterm birth or on later wheezing were chosen (web figure 1).(28-31) All the parameters were included in an initial multivariable model and only the parameters with a suggestive evidence of association based on $P < 0.1$ were included in the final multivariable model.

Analyses were performed using LatentGOLD 5.1 and PASW 20 (SPSS Inc. Chicago, Illinois.).

RESULTS

From 19,244 families, data were available from 18,552 (96.4%), 15,590 (81.0%), 15,246 (79.2%), 13,857 (72.0%) and 13,287 (69%) families at 9 months and 3, 5, 7, 11 years respectively. From 19,517 children in the original cohort, 18,565 (95.1%) had data on gestational age. 1,502 (8.1%) children were born preterm, of which 1,049 (69.8%) had recent-wheeze data for at least three time-points thus were included in the phenotype analyses. From 17,063 term-born children, data for phenotype analyses were available for 12,307 (72.1%). Web table 1 compares included and excluded children and Table 1 compares included preterm- and term-born children. Included preterm-born children had lower birth-weight and gestational age; were less likely to be breast-fed; had fewer siblings and lower rates of childcare than included term-born children. However, they had higher rates of IUGR, caesarean section, neonatal unit admissions, hospital stays, asthma-diagnosis and antenatal maternal smoking; and, a greater percentage of maternal body mass index was outside the normal range compared to term-born children. Socio-economic status was similar.

794 (75.7%) and 255 (24.3%) of preterm-born and 9,526 (77.4%) and 2,781 (22.6%) of term-born children had wheezing data at all 4 or at 3 time-points respectively. Recent-wheeze was greater at all time-points in the preterm-born group than term-born group although the association was weaker at 11 years (Table 2). In general, there was a gradient, with odds ratios (OR) for recent-wheeze increasing with decreasing gestation (web table 2).

Four phenotypes were defined as shown in Figure 1. (See web appendix 1 for their derivation):

- No/infrequent – no or infrequent wheezing through the four-time points. Wheezing at none of the time points or at one time point only.
- Early-wheeze – wheezing reported at 3 year of age and disappearing by 7 or 11 years of age.
- Persistent-wheeze – wheezing which persisted throughout the study period.
- Late-wheeze – no wheeze reported before the age of 7 years but developing at 7 years or beyond.

Table 3 compares the wheezing-phenotypes between the preterm- and term-born children. Preterm children were more likely to develop early (OR 1.6, 95% confidence interval: 1.3 to 1.9, *P* <0.001) and persistent (1.6, 1.3 to 1.9, *P*<0.001) wheeze but not late-wheeze (1.0, 0.7 to 1.5, *P* =0.90), when compared to term-born children.

Whilst most demographic characteristics were similar between the different wheezing-phenotypes (web table 3), birth-weight, gestational age at birth, antenatal smoking, neonatal unit admissions, length of hospital stay, asthma-diagnosis, maternal atopy, and child's atopy were different between the wheezing-phenotypes although differences for gestational age were marginal. Furthermore, antenatal smoking and neonatal unit admission were highest in the late-wheeze group; antenatal smoking was lowest in the persistent-wheeze group; and length of hospital stay was highest in the early-wheeze group. Atopy and asthma-diagnosis were highest in the persistent-wheeze group.

Next, all early life factors and characteristics were included in an initial multi-nomial model then only those suggestive of an association were included in the final multi-nomial model for preterm (Table 4) and term groups (Table 5). Preterm- and term-born children who were exposed to antenatal maternal smoking, were male, or who had atopy had higher ORs for all the wheezing-phenotypes. Formal childcare was associated with higher ORs for early-wheeze in both preterm- and term-born children. The association between term-born children and antenatal maternal smoking were stronger but the ORs were generally low. The strongest association for atopy for both preterm- and term-born children was with persistent-wheeze. Preterm children born at 24-32 weeks' gestation had higher ORs for all the wheezing-phenotypes. The 24-32 weeks' gestation band had higher ORs for all phenotypes compared to the 33-34 weeks' gestation group. Preterm children born with IUGR; had higher ORs for all the wheezing-phenotypes. However, IUGR in term-born children led to a slightly increased risk of early and persistent-wheeze but a lower risk of late-wheeze. Maternal atopy was associated with higher OR for persistent-wheeze in the preterm group and higher ORs for all wheezing-phenotypes in term-born children. Breast feeding in preterm-born was weakly associated with lower ORs for early and persistent but not late-wheeze which had a higher OR; in term-born children breast-feeding was weakly associated with lower ORs for all the wheezing-phenotypes. The small numbers in the mothers' age band and mothers' body mass index groups made it difficult to interpret the results. In term-born children, only delivery by caesarean section, or exposure to damp or having siblings were weakly associated with an increased risk of early and persistent-wheeze.

DISCUSSION

Using a well-established cohort with longitudinal data, we noted that rates of recent-wheeze in preterm-born children when compared to term-born children, were increased at each time-point (although the association was weaker at 11 years) as previously reported.(8, 32) We also defined four wheezing-phenotypes as recently reported in largely term-born children in the MCS.(33) The ORs for early- and persistent-wheeze were greater in the preterm group but late-wheeze was similar in both groups. Early life factors and characteristics, especially antenatal maternal smoking, atopy and male gender, were associated with wheezing-phenotypes in both preterm and term groups and breast feeding was associated with decreased rates of wheezing-phenotypes in both groups except for late-wheeze in the preterm-born children, although the magnitude of association by various early life factors and characteristics varied between the groups. However, prematurity was associated with increased rates of wheezing in the early and persistent groups but not the late-wheeze group suggesting that delivery at an early stage of lung development is a risk factor for the development of certain wheezing-phenotypes.

In line with previous reports,(8) we also noted greater recent-wheeze in preterm-born children than in term-born children, although similar wheezing-phenotypes developed in both groups. It has been assumed that respiratory symptoms and lung function deficits commence in infancy and continue into later life given the accepted concept of tracking of lung function.(34) This concept is perhaps not surprising given the delivery of preterm infants at an early stage of lung development.(19) It has been assumed that post-natal lung growth and development, especially, when exposed to noxious substances such as supplemental oxygen therapy,(35) is abnormal placing these children at future risk of chronic obstructive pulmonary disease.(18) We noted that the majority of preterm-born children commenced their respiratory symptoms in early childhood but there was a group who had late-wheeze comparable to term-born children. The group of very preterm-born children was associated with an increased risk of all the wheezing-phenotypes. Encouragingly, from those reporting early-wheeze, over half had early-wheeze which ameliorated with time. Taken together, these data suggest that wheezing in preterm-born children is a heterogeneous disease process in which continuing growth and remodelling of the airways and parenchyma in childhood results in decreased symptoms in many.(36) Since some wheezing-phenotypes in largely term-born children are associated with lung function deficits (especially persistent-wheeze),(12, 14, 16, 17) it will be important to investigate if similar lung deficits are associated with particular wheezing-phenotypes of preterm-born children. As suggested for asthma, the underlying mechanisms or endotypes (37, 38) and responses to treatment may be different for each wheezing-phenotype in preterm-born children. Although, treatment for prematurity-associated wheeze remains uncertain.(39)

We had anticipated that wheezing would be persistent in very preterm-born children especially as many of these infants are exposed to noxious substances.(35) However, we were surprised to note similar gestational age between the different phenotypes. As we did not have comprehensive early neonatal data, we were unable to determine if early life factors and exposures could be associated with the development of a particular wheeze phenotype. Nevertheless, the combination of these factors often results in development of bronchopulmonary dysplasia in infancy/ chronic lung disease of prematurity which is associated with greater respiratory symptoms and lung function decrements (2).

When only the early life factors and characteristics were investigated, similar associations were observed between antenatal smoking, formal childcare, male gender and child's atopy and the wheezing-phenotypes in both groups. Differences, albeit marginal, were observed for IUGR, breast feeding, delivery by caesarean section, having siblings, exposure to damp and maternal atopy and the wheezing-phenotypes for preterm and term born children. All wheezing-phenotypes in both groups were associated with atopy but was greatest for persistent-wheeze in both groups. Similar observations have been made for phenotypes in a birth cohort of mainly term-born children;(14) and a systematic review reporting factors predicting persistence of early-wheeze noted atopy was amongst the most frequently identified factor.(40)

Wheezing-phenotypes have been described in cohorts of mainly term-born children.(12-15) Our observations suggest that prematurity is also associated with differing phenotypes with some that resolve or decrease in prevalence (early), continue (persistent) or develop later (late). Caudri et al reported additional risk factors associated with the wheezing-phenotype, interestingly caesarean section was not associated.(41) This is in line with our recent study reporting that caesarean section was not strongly associated but the relative immaturity of the early-term born infant was important.(10) However, we did observe an association between delivery by caesarean section and early and persistent-wheeze in term-born children.

Modelling for the preterm-born children only showed that child's atopy and antenatal smoking were associated with an increased risk of all the wheezing-phenotypes. This is in line with an analysis of eight birth cohorts containing term- and preterm-born children which concluded there was an increased risk of wheeze and asthma amongst children who were exposed to maternal smoking during pregnancy, but were not exposed after birth.(31) In addition to the associations of in-utero smoke on the child's lung development it leads to an increased rate of preterm-birth.(42) A study of largely term-born children suggested that inherited factors are a primary cause of late-onset persistent-wheeze. However, environmental exposure in early life may combine with inherited factors resulting in early-onset persistent-wheeze.(30) Another study identified some modifiable factors in infancy such as household dampness and breast-feeding.(29)

The strength of the study is the inclusion of a large number of preterm-born children with longitudinal data. We, however, did not have comprehensive early neonatal data, formal allergen testing or lung function measures which would have enabled association of lung function deficits with particular wheezing-phenotypes as observed in term-born children.(43) A limitation is that early neonatal data were not available for the preterm group including need for mechanical ventilation, surfactant treatment, development of bronchopulmonary dysplasia in infancy, and length of oxygen supplementation, especially as these factors could potentially have been relevant to the types of wheezing phenotype that the preterm-born child may have developed. A limitation of this prospective study is that the wheeze data is self-reported. However, the questions used are taken from the International Study of Asthma and Allergies in Childhood.(44) The questionnaire is a widely used, well respected and validated questionnaire. Jenkins et al. reported that the questionnaire showed high agreement with doctor-diagnosed asthma symptoms.(45) Shaw et al. also validated the questionnaire and reported it was effective in measuring the bronchial hyper-responsiveness prevalence.(46) A study in Brazil concluded that the asthma section was reproducible and could separate out asthmatics and controls.(47). In agreement, a Finish study reported that the ISAAC questionnaire was highly validated.(48) Loss to follow up was a further limitation.

Conclusion

We have defined wheezing-phenotypes for preterm-born children for the first time. Encouragingly, a large proportion of preterm-born children have early-wheeze which improves with age. Although, this is may not be true for very preterm-born children as reported in some other studies. Early life factors and characteristics appeared to have similar associations on wheezing-phenotypes in both preterm and term groups. However, the ORs were greater in the preterm-group especially for early- and persistent-wheeze. The underlying mechanisms of why preterm develop lung disease are unclear but for both groups it is clear that avoidance of risk factors such as antenatal smoking or exposure to beneficial ones such as breast feeding are important.

Acknowledgement

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SJK reports support from Nutricia Research Foundation for performing this study. SK reports funding from Medical Research Council (MRC) (MR/M022552/1) for this submitted work; and grants from National Institute for Health Research (NIHR) (16/111/106), Welsh Government, and European Commission (EU) FP7 outside of this submitted work. There was no study sponsor involvement in the study design, the collection, analysis, and interpretation of data; the writing of the report; and the decision to submit the manuscript for publication.

We are grateful to the Centre for Longitudinal Studies (CLS), Institute of Education for the use of these data and to the UK Data Service for making them available, and to the children and families who take part in the study. However, neither CLS nor the UK Data Service bears any responsibility for the analysis or interpretation of these data. The results have been presented at the European Respiratory Society in Paris 15-19th September 2018. SK, SJK, JL, WJW, AJH, RG report no conflicts of interest.

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TABLES

Table 1 – Demographics of Preterm and Term Children with Wheezing-Phenotype Data, United Kingdom, Year of Birth 2000-2002.

Demographic	**Preterm-born children n =1,049**				**Term-born children n =12,307**				***P* value**
	Number	**Percentage**	**Mean**	**SD**	**Number**	**Percentage**	**Mean**	**SD**	
Mean birth-weight (kg) [b]			2.33	0.68			3.43	0.51	0.00
Mean birth-weight (z-score)			0.01	1.20			-0.03	1.00	0.18
Mean gestation (weeks) [b]			34.3	2.4			39.8	1.3	0.00
24-28 weeks' gestation	50	4.8							
24-32 weeks' gestation	192	18.3							
Male	536	51.1			6,202	50.4			0.66
IUGR at birth [b c]	145/1,048	13.8			1,238/12,300	10.1			0.00
Antenatal maternal smoking [b c]	408/1,047	39.0			3,980/12,291	32.4			0.00
Antenatal smoke exposure [b c]									0.00
none	639/1,047	61.0			8,311/12,291	67.6			
1-9 cigarette	106/1,047	10.1			1,041/12,291	8.5			
10-19 cigarette	171/1,047	16.3			1,725/12,291	14.0			
>/= 20 cigarette	131/1,047	12.5			1,214/12,291	9.9			
Socio-economic status [c]									0.81
Management/Professional	299/945	31.6			3,655/11,109	32.9			
Intermediate	178/945	18.8			2,148/11,109	19.3			

Self employed	38/945	4.0			464/11,109	4.2			
Supervisory/Technical	55/945	5.8			663/11,109	6.0			
Semi routine/routine	375/945	39.7			4,179/11,109	37.6			
Breast-fed [b c]	688	65.6			8,493/12,306	69.0			0.02
Ethnicity white [c]	881/1,048	84.1			10,416/12,284	84.8			0.53
Caesarean section [b c]	458/1,048	43.7			2,516/12,252	20.5			0.00
Admitted to neonatal unit[bc]	541/1,048	51.6			710	5.8			0.00
Length of stay after birth (days) [b]			17.6	24.3			3.1	5.8	0.00
Exposure to smoking after birth	317	30.2			3,436	27.9			0.11
Atopy at any age	623	59.4			7,377	59.9			0.73
Asthma-diagnosis [b]	339	32.3			2,969	24.1			0.00
Maternal age at child's birth (yrs)			29.1	6.1			28.8	5.8	0.16
Maternal history of atopy									0.13
Missing	1	0.0			9	0.0			
Asthma and Eczema	73	7.0			697	5.7			
Asthma or Eczema	243	23.2			2,716	22.1			
None	732	69.8			8,885	72.2			
Maternal body mass index before pregnancy[a]			23.8	5.2			23.8	4.4	0.86
Maternal body mass index group before pregnancy [b]									0.00
Refusal	0	0.0			2	0.0			

Not available	91	8.7			960	7.8			
Underweight	74	7.1			593	4.8			
Normal weight	613	58.4			7396	60.1			
Overweight	165	15.7			2368	19.2			
Obese	92	8.8			906	7.4			
Morbidly Obese	14	1.3			82	0.7			
Damp or condensation exposure [c]	126	12.0			1,654/12,285	13.5			0.18
Pollution, grime and environmental problems [c]									0.51
Very common	70/1,038	6.7			749/12,183	6.1			
Fairly common	150/1,038	14.5			1,943/12,183	15.9			
Not very common	403/1,038	38.3			4,773/12,183	39.2			
Not at all common	415/1,038	40.0			4,718/12,183	38.7			
Number of siblings in household mean [b]			0.86	1.1			0.93	1.0	0.03
Childcare [b c]									0.00
Formal	135/1,043	12.9			1,758/12,276	14.3			
Informal	284/1,043	27.2			3,882/12,276	31.6			

IUGR=intrauterine growth restriction
[a] Weight (kg)/height(m)^2
[b] *P* <0.05 between the term and preterm children with wheezing-phenotype data
[c] There is missing data for some of the variables

Table 2 – Unadjusted Association between Preterm/Term Birth and Recent Wheezing (in the past 12 months) at Each Age. United Kingdom, Year of Birth 2000-2002

Age (years)	Preterm			Term			OR	95% CI	*P*-value
	Number	Total number	Percentage	Number	Total Number	Percentage			
3 [a]	259	984	26.3	2,228	11,584	19.2	1.5	1.3,1.7	<0.001
5 [a]	232	1,022	22.7	1,907	12,003	15.9	1.6	1.3,1.8	<0.001
7 [a]	150	990	15.2	1,402	11,743	11.9	1.3	1.1,1.6	<0.005
11 [a]	131	945	13.9	1,314	11,117	11.8	1.2	1.0,1.5	0.06
Any time-point	443	1,049	42.2	3,993	12,307	32.4	1.5	1.3,1.7	<0.001

OR - odds ratio

CI - confidence interval

[a] There is missing data for some of the variables

Table 3 – Unadjusted Associations Between Preterm/Term Birth and Wheezing-Phenotypes. United Kingdom, Year of Birth 2000-2002

Wheezing Phenotype	Preterm children		Term children		Total	OR (95% CI)	95% CI	*P*-value
	Number	Percentage	Number	Percentage				
No wheeze	693	66.1	9,193	74.7	9,886	1 (ref)		
Early-wheeze	189	18.0	1,597	13.0	1,786	1.6	1.3,1.9	<0.001
Persistent-wheeze	137	13.1	1,131	9.2	1,268	1.6	1.3,1.9	<0.001
Late-wheeze	30	2.9	386	3.1	416	1.0	0.7,1.5	0.90
Total	1,049		12,307		13,356			

OR - odds ratio

CI - confidence interval

Table 4 Adjusted Associations Between Early Risk Factors and characteristics and Wheezing-Phenotypes Using the No/Infrequent Wheezing-Phenotype as the Reference Category for Preterm-Born Children (Complete Cases Only). United Kingdom, Year of Birth 2000-2002

Early Risk Factor		**Early-wheeze (n=160)**			**Persistent-wheeze (n=113)**			**Late-wheeze (n=22)**		
	Number [a]	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***
Mothers' body mass index Under weight	53	2.124	1.053,4.285	0.04	1.291	0.523, 3.182	0.58	1.882	0.390, 9.085	0.43
Over weight	156	1.843	1.170,2.901	0.01	1.135	0.633, 2.033	0.67	0.284	0.037,2.212	0.23
Obese	84	1.006	0.505,2.004	0.99	1.389	0.696, 2.775	0.35	1.842	0.567,5.984	0.31
Morbidly Obese	14	1.679	0.463,6.085	0.43	0.960	0.186, 4.958	0.96	N/A		.
Normal	546	1.0	Referent		1.0	Referent		1.0	Referent	
Gestation band 24-32 weeks	158	2.010	1.257,3.215	0.00	1.798	1.044, 3.098	0.03	2.458	0.897, 6.730	0.08
33-34 weeks	202	1.090	0.696,1.708	0.71	0.822	0.476, 1.420	0.48	0.898	0.276,2.926	0.86
35-36 weeks	493	1.0	Referent		1.0	Referent		1.0	Referent	
Breast-feeding Yes	571	0.676	0.457,1.00	0.05	0.816	0.514,1.298	0.39	1.288	0.471,3.518	0.62
No	282	1.0	Referent		1.0	Referent		1.0	Referent	
IUGR Yes	117	1.619	0.981,2.669	0.06	1.352	0.724, 2.528	0.34	1.248	0.345, 4.513	0.74
No	736	1.0	Referent		1.0	Referent		1.0	Referent	
Antenatal Smoking Yes	325	1.670	1.131,2.466	0.01	1.482	0.938,2.342	0.09	2.153	0.850,5.453	0.11
No	528	1.0	Referent		1.0	Referent		1.0	Referent	
Childcare Formal	131	1.709	1.008,2.897	0.05	1.094	0.572,2.093	0.79	1.059	0.270,4.152	0.93
Informal	260	1.091	0.715,1.644	0.69	0.938	0.576,1.529	0.80	0.674	0.233, 1.946	0.47
None	462	1.0	Referent		1.0	Referent		1.0	Referent	
Mothers' age bands </=19	52	0.843	0.335,2.122	0.72	1.737	0.708,4.259	0.23	0.570	0.065,4.970	0.61
20-24	113	1.793	0.996,3.227	0.05	1.623	0.801,3.290	0.18	0.645	0.129,3.230	0.59

30-34	277	1.138	0.697, 1.859	0.61	1.558	0.901,2.694	0.11	1.120	0.394,3.184	0.83
35-39	131	1.803	1.025, 3.171	0.04	1.481	0.735,2.985	0.27	0.630	0.125,3.171	0.58
40 plus	26	2.308	0.873, 6.099	0.09	0.903	0.188,4.329	0.90	1.754	0.192,16.070	0.62
25-29	254	1.0	Referent		1.0	Referent		1.0		
Maternal atopy	254	0.984	0.650,1.490	0.94	1.569	1.006,2.447	0.05	0.976	0.363,2.622	0.96
Yes										
No	599	1.0	Referent		1.0	Referent		1.0	Referent	
Gender	440	1.12	0.775,1.618	0.55	1.803	1.169,2.779	0.01	1.566	0.643,3.814	0.32
Male										
Female	413	1.0	Referent		1.0	Referent		1.0	Referent	
Child Atopy	507	1.487	1.019, 2.169	0.04	4.432	2.597,7.563	0.00	2.416	0.906,6.440	0.08
Yes										
No	346	1.0	Referent		1.0	Referent		1.0	Referent	

IUGR=intrauterine growth restriction

[a]Total number includes those in no/infrequent wheeze group

Table 5 Adjusted Associations Between Early Risk Factors and characteristics and Wheezing-Phenotypes Using the No/Infrequent Wheezing-Phenotype as the Reference Category for Term-Born Children (Complete Cases Only). United Kingdom, Year of Birth 2000-2002

Early Risk Factor		Early-wheeze (n=1,325)			Persistent-wheeze (n=943)			Late-wheeze (n=309)		
	Number[a]	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
Mothers' body mass index										
Under weight	474	1.294	1.001, 1.673	0.05	0.906	0.636, 1.291	0.59	0.872	0.466, 1.630	0.67
Over weight	2,122	1.086	0.934, 1.263	0.28	1.300	1.099, 1.538	0.00	1.163	0.877, 1.543	0.29
Obese	839	1.229	0.995, 1.519	0.06	1.214	0.948, 1.556	0.12	1.280	0.857, 1.911	0.23
Morbidly Obese	68	1.761	0.950, 3.266	0.07	1.096	0.480, 2.501	0.83	1.471	0.446, 4.854	0.53
Normal	6,676	1.0	Referent		1.0	Referent		1.0	Referent	
Pollution										
Very Common	607	0.981	0.756, 1.272	0.88	1.213	0.909, 1.619	0.19	0.920	0.561,1.510	0.74
Fairly Common	1,520	1.052	0.881, 1.256	0.57	1.219	0.995, 1.493	0.06	0.814	0.571,1.162	0.26
Not very common	3,932	0.992	0.868, 1.134	0.91	1.045	0.890, 1.226	0.59	0.792	0.612,1.026	0.08
Not at all common	4,120	1.0	Referent		1.0	Referent		1.0	Referent	
Damp										
Yes	1,270	1.100	0.925, 1.310	0.28	1.212	0.992,1.480	0.06	0.911	0.629, 1.320	0.62
No	8,909	1.0	Referent		1.0	Referent		1.0	Referent	
Childcare										
Formal	1,626	1.253	1.038, 1.512	0.02	0.742	0.585, 0.940	0.01	0.918	0.639, 1.320	0.65
Informal	3,573	1.052	0.918, 1.205	0.47	0.912	0.779, 1.067	0.25	0.924	0.711, 1.201	0.56
None	4,980	1.0	Referent		1.0	Referent		1.0	Referent	
Breast-feeding										
Yes	7,142	0.849	0.743, 0.971	0.02	0.825	0.704, 0.967	0.02	0.855	0.657, 1.112	0.24
No	3,037	1.0	Referent		1.0	Referent		1.0	Referent	
IUGR										
Yes	934	1.198	0.986, 1.455	0.07	1.092	0.859, 1.387	0.47	0.366	0.199, 0.675	0.00
No	9,245	1.0	Referent		1.0	Referent		1.0	Referent	
Antenatal Smoking										
Yes	3,316	1.207	1.058, 1.378	0.01	1.206	1.031, 1.410	0.02	1.427	1.105, 1.842	0.01
No	6,863	1.0	Referent		1.0	Referent		1.0	Referent	
Mothers' age bands										
</=19	563	1.269	0.968, 1.664	0.09	0.726	0.502, 1.050	0.09	0.675	0.365, 1.247	0.21

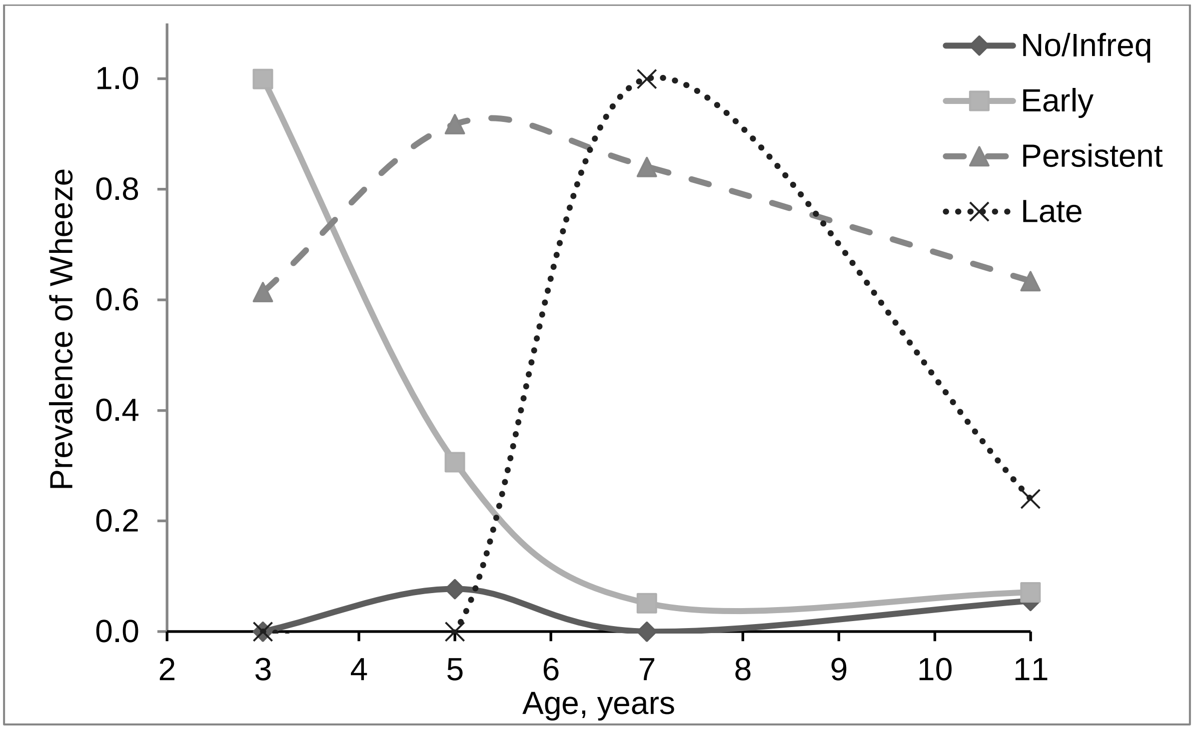
20-24	1,610	1.212	1.010, 1.454	0.04	1.170	0.945, 1.447	0.15	0.687	0.455, 1.037	0.07
30-34	3,315	0.888	0.758, 1.041	0.14	0.842	0.699, 1.015	0.07	1.180	0.876, 1.588	0.28
35-39	1,596	0.794	0.648, 0.974	0.03	0.964	0.768, 1.211	0.75	1.288	0.897, 1.851	0.17
40 plus	241	1.381	0.949, 2.008	0.09	1.470	0.959, 2.255	0.08	1.863	0.936, 3.707	0.08
25-29	2,854	1.0	Referent		1.0	Referent		1.0	Referent	
Social Class										
Highest (1)	3,408	0.833	0.702, 0.990	0.04	1.007	0.825, 1.230	0.94	0.815	0.592, 1.122	0.21
2	1,991	0.869	0.730, 1.033	0.11	0.989	0.807, 1.213	0.92	0.855	0.613,1.192	0.35
3	420	0.898	0.653, 1.234	0.51	1.045	0.722, 1.512	0.82	0.314	0.126,0.784	0.01
4	615	0.763	0.584, 0.997	0.05	1.050	0.784, 1.405	0.75	0.774	0.459, 1.306	0.34
Lowest (5)	3,745	1.0	Referent		1.0	Referent		1.0	Referent	
Maternal atopy										
Yes	2,903	1.537	1.355, 1.744	0.00	1.604	1.386, 1.856	0.00	1.228	0.955, 1.578	0.11
No	7,276	1.0	Referent		1.0	Referent		1.0	Referent	
Siblings										
Yes	5,865	1.251	1.092,1.433	0.00	1.142	0.975, 1.338	0.10	0.948	0.730, 1.229	0.69
No	4,314	1.0	Referent		1.0	Referent		1.0	Referent	
Caesarean Section										
Yes	2,099	1.069	0.920, 1.241	0.38	1.204	1.017, 1.425	0.03	0.865	0.644,1.161	0.33
No	8,080	1.0	Referent		1.0	Referent		1.0	Referent	
Gender										
Male	5,138	1.266	1.125, 1.426	0.00	1.640	1.423, 1.890	0.00	1.278	1.016, 1.609	0.04
Female	5,041	1.0	Referent		1.0	Referent		1.0	Referent	
Child Atopy										
Yes	6,122	1.477	1.304, 1.672	0.00	4.559	3.773, 5.509	0.00	2.665	2.031,3.496	0.00
No	4,057	1.0	Referent		1.0	Referent		1.0	Referent	

IUGR=intrauterine growth restriction

[a]Total number includes those in no/infrequent wheeze group

FIGURES

Figure 1 – Wheezing-Phenotypes for Preterm-Born Children. United Kingdom, Year of Birth 2000-2002



Web Material

Comparison of the Associations of Early Life Factors on Wheezing-Phenotypes in Preterm-Born Children and Term-Born Children

Sarah J Kotecha, W John Watkins, John Lowe, Raquel Granell, A John Henderson, and Sailesh Kotecha.

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Web Appendix 1

METHODS

MCS is a cohort of 19,517 children born in the UK between 2000-2002. The children were selected through the Child Benefit system with over-sampling from Wales, Scotland and Northern Ireland. Oversampling also occurred from areas with higher concentrations of Black and Asian families, and from deprived areas.

All data were collected at face-to-face interviews. At nine months of age, data were collected on pregnancy, birth and early life including breast feeding (breast milk intake for any period of time), any antenatal maternal smoking and socio-economic status (based on main carer's last known job), delivery by caesarean section (CS), exposure to damp or condensation, exposure to pollution, grime and environmental problems, number of siblings, childcare use (informal e.g. family members and formal e.g. childminder, nursery etc.), maternal history of atopy (none, asthma and eczema, asthma or eczema), maternal pre-pregnancy body mass index (BMI) (underweight, normal, overweight, obese, morbidly obese), maternal age at birth of child. At 3, 5, 7 and 11 years of age, longitudinal data were collected for respiratory symptoms (including wheeze ever and recent wheeze – defined as parental reporting of wheezing or whistling in the chest – in the last 12 months), asthma-diagnosis (based on parental reports) and child's atopic diseases (diagnosis of eczema and hay fever), exposure to smoking (positive if exposure occurred at any time-point in the same room as the child). Ethnicity was coded as Caucasian or non-Caucasian.

Statistical Analysis

We, used LatentGOLD 5.1 (Statistical Innovations, Boston, Ma., USA) to define the optimal number of phenotypes to study. Children reporting recent-wheeze for at least three time-points were assigned a 4-digit string with the digits assigned 1 or 0 for recent-wheeze at 3, 5, 7 and 11 years. Thus "0000" signified never wheezed and "1111" signified wheezing at all-time points. Where there were three reports of recent-wheeze, the missing time period was assigned an "asterisk". For the term and preterm-born children who had data available at 3 or 4 time points 4 classes were chosen as the first non-significant p-value and the lowest BIC. The class posterior probability was used to assign each wheezing pattern to the class of wheezing-phenotype which they had the highest probability of belonging to. The machine driven approach was used for all the wheezing patterns.

Web Appendix 2

RESULTS

Web Table 1

Web Table 1 compares children who were or were not included. A greater percentage of preterm- and term-born children for whom wheezing data were not available were male, from lower socio-economic classes, had lower rates of breast-fed or asthma-diagnosis, less exposure to post-natal smoking, had younger mothers, a greater percentage of maternal BMIs were outside the normal weight range, were more likely to be from an ethnic minority, were more likely to be exposed to pollution, grime and environmental problems, had lower rates of being in formal or informal childcare but were less likely to be atopic. The term-born children not included also had lower birth-weight z-score and higher exposure to antenatal maternal smoking and had more siblings in the household.

Web Tables

Web Table 1 – Demographics of the Preterm- and Term-Born Children With and Without Wheezing-Phenotype Data. United Kingdom, Year of Birth 2000-2002

	Term children with wheezing phenotype data	**Term children without wheezing phenotype data**	**Preterm children with wheezing phenotype data**	**Preterm children without wheezing phenotype data**
Number	12,307	4,756	1,049	453
Mean birth-weight (kg) (SD)[$]	3.43 (0.51)	3.39 (0.51)	2.33 (0.68)	2.35 (0.72)
Mean birth-weight (z-score) (SD)[$]	-0.03 (1.00)	-0.08 (1.01)	0.01 (1.20)	0.04 (1.23)
Mean gestation (weeks) (SD)[$]	39.81 (1.27)	39.72 (1.29)	34.34 (2.43)	34.18 (2.68)
IUGR at birth N (%)	1,238/12,300 (10.1)	517/4,750 (10.9)	145/1,048 (13.8)	58/453 (12.8)
Male N (%) [$*]	6,202/12,307 (50.4)	2,501/4,756 (52.6)	536/1,049 (51.1)	268/453 (59.2)
Antenatal maternal smoking N (%)[$]	3,980/12,291(32.4)	1,892/4,748 (39.8)	408/1,047 (39.0)	181/452 (40.0)
Antenatal smoke exposure N (%)[$]				
none	8,311/12,291 (67.6)	2,856/4,748 (60.2)	639/1,047 (61.0)	271/452 (60.0)
1-9 cigarette	1,041/12,291 (8.5)	525/4,748 (11.1)	106/1,047 (10.1)	46/452 (10.2)
10-19 cigarette	1,725/12,291 (14.0)	816/4,748 (17.2)	171/1,047 (16.3)	69/452 (15.3)
>/= 20 cigarette	1,214/12,291 (9.9)	551/4,748 (11.6)	131/1,047 (12.5)	66/452 (14.6)
Socio-economic status N (%)[$*]				
Management/Professional	3,655/11,109 (32.9)	841/3,997 (21.0)	299/945 (31.6)	89/389 (22.9)
Intermediate	2,148/11,109 (19.3)	733/3,997 (18.3)	178/945 (18.8)	69/389 (17.7)
Self employed	464/11,109 (4.2)	142/3,997 (3.6)	38/945 (4.0)	7/389 (1.8)
Supervisory/Technical	663/11,109 (6.0)	252/3,997 (6.3)	55/945 (5.8)	25/389 (6.4)
Semi routine/routine	4,179/11,109 (37.6)	2,029/3,997 (50.8)	375/945 (39.7)	199/389 (51.2)
Breast fed N (%) [$*]	8,493/12,306 (69.0)	2,740/4,753 (57.6)	688/1,049 (65.6)	267/453 (58.9)
Ethnicity white N (%) [$*]	10,416/12,284 (84.8)	3,724/4,751 (78.4)	881/1,048 (84.1)	353/453 (77.9)
Caesarean section N (%)	2,516/12,252 (20.5)	1,000/4,739 (21.1)	458/1,048 (43.7)	194/453 (42.8)
Admitted to NNU N (%)[$]	710/12,307 (5.8)	297/4,751 (6.3)	541/1,048 (51.6)	223/453 (49.2)
Length of stay after birth (days) (SD)*	3.12 (5.81)	3.25 (6.09)	17.63 (24.31)	21.45 (34.91)
Exposure to smoking after birth N (%)[$*]	3,436/12,307 (27.9)	1,090/4,755 (22.9)	317/1,049 (30.2)	103/452 (22.8)
Atopy at any age N (%)[$*]	7,377/12,307 (59.9)	1,253/2,978 (42.1)	623/1,049 (59.4)	116/291 (39.9)
Asthma-diagnosis N (%)[$*]	2,969/12,307 (24.1)	527/2,973 (17.7)	339/1,049 (32.3)	69/291 (23.7)
Maternal age at child's birth (yrs) (SD) [*$]	28.8 (5.8)	27.2 (6.1)	29.1 (6.1)	27.3 (6.4)
Maternal history of atopy N (%)				
Missing	9/12,307 (0.0)	1/4,756 (0.0)	1/1,049 (0.0)	0/453 (0)
Asthma and Eczema	697/12,307 (5.7)	264/4,756 (5.6)	73/1,049 (7.0)	28/453 (6.2)

Asthma or Eczema	2,716/12,307 (22.1)	980/4,756 (20.6)	243/1,049 (23.2)	83/453 (18.3)
None	8,885/12,307 (72.2)	3,511/4,756 (73.8)	732/1,049 (69.8)	342/453 (75.5)
Maternal's BMI before child's pregnancy (kg/m^2) (SD) *$	23.8 (4.4)	23.4 (4.3)	23.7 (5.2)	23.1 (4.9)
Maternal BMI group before pregnancy N (%)*$				
Refusal	2/12,307 (0)	2/4,756 (0)	0/1,049 (0)	0/453 (0)
Not applicable	960/12,307 (7.8)	480/4,756 (10.1)	91/1,049 (8.7)	51/453 (11.3)
Underweight	593/12,307 (4.8)	307/4,756 (6.5)	74/1,049 (7.1)	44/453 (9.7)
Normal weight	7,396/12,307 (60.1)	2,798/4,756 (58.8)	613/1,049 (58.4)	252/453 (55.6)
Overweight	2,368/12,307 (19.2)	809/4,756 (17.0)	165/1,049 (15.7)	78/453 (17.2)
Obese	906/12,307 (7.4)	338/4,756 (7.1)	92/1,049 (8.8)	22/543 (4.9)
Morbidly Obese	82/12,307 (0.7)	22/4,756 (0.5)	14/1,049 (1.3)	6/453 (1.3)
Damp or condensation exposure N (%)	1,654/12,285 (13.5)	682/4,738 (14.4)	126/1,049 (12.0)	69/452 (15.3)
Pollution, grime and environmental problems N (%)*$				
Very common	749/12,183 (6.1)	320/4,685 (6.8)	70/1,038 (6.7)	39/449 (8.7)
Fairly common	1,943/12,183 (15.9)	818/4,685 (17.5)	150/1,038 (14.5)	72/449 (16.0)
Not very common	4,773/12,183 (39.2)	1,789/4,685 (38.2)	403/1,038 (38.3)	195/449 (43.4)
Not at all common	4,718/12,183 (38.7)	1,758/4,685 (37.5)	415/1,038 (40.0)	143/449 (31.8)
Number of siblings in household N$	0.93 (1.0)	0.97 (1.1)	0.86 (1.1)	0.87 (1.1)
Childcare N (%)*$				
Formal	1,758/12,276 (14.3)	376/4,749 (8.0)	135/1,043 (12.9)	35/451 (7.8)
Informal	3,882/12,276 (31.6)	1,248/4,749 (26.3)	284/1,043 (27.2)	105/451 (23.3)

IUGR= intrauterine growth restriction

$ ***P*** <0.05 between those with and without wheezing-phenotype data for the term children

* ***P*** <0.05 between those with and without wheezing-phenotype data for the preterm children

Web Table 2 – Unadjusted Odds Ratio of Recent Wheeze at Each Age for Each Gestation Band Against Term. United Kingdom, Year of Birth 2000-2002.

Gestation group	3 years of age (N)	Odds ratio (95% CI)	*P* -value
24-32 weeks	62/181 (34.3%)	2.2 (1.6, 3.0)	<0.0001
33-34 weeks	62/233 (26.6%)	1.5 (1.1, 2.0)	0.0051
35-36 weeks	135/570 (23.7%)	1.3 (1.1, 1.6)	0.0089
Term	2,228/11,584 (19.2%)	ref	Ref

Gestation group	**5 years of age (N)**	**Odds ratio (95% CI)**	***P* -value**
24-32 weeks	47/186 (25.3%)	1.8 (1.3, 2.5)	0.0006
33-34 weeks	58/240 (24.2%)	1.7 (1.3, 2.3)	0.0006
35-36 weeks	127/596 (21.3%)	1.4 (1.2, 1.8)	0.0005
Term	1,907/12,003 (15.9%)	ref	ref

Gestation group	**7 years of age (N)**	**Odds ratio (95% CI)**	***P* -value**
24-32 weeks	36/178 (20.2%)	1.9 (1.3, 2.7)	0.0009
33-34 weeks	31/232 (13.4%)	1.1 (0.8, 1.7)	0.51
35-36 weeks	83/580 (14.3%)	1.2 (1.0, 1.6)	0.09
Term	1,402/11,743 (11.9%)	ref	Ref

Gestation group	**11 years of age (N)**	**Odds ratio (95% CI)**	***P* -value**
24-32 weeks	33/177 (18.6%)	1.7 (1.2,2.5)	0.006
33-34 weeks	31/221 (14.0%)	1.2 (0.8,1.8)	0.32
35-36 weeks	67/547 (12.2%)	1.0 (0.8, 1.4)	0.76
Term	1,314/11,117 (11.8%)	ref	Ref

Gestation group	**Any wheeze at any time point (N)**	**Odds ratio (95% CI)**	**p-value**
24-32 weeks	101/192 (52.6%)	2.3 (1.7, 3.1)	<0.0001
33-34 weeks	102/249 (41.0%)	1.4 (1.2, 1.9)	0.0047
35-36 weeks	240/608 (39.5%)	1.4 (1.1, 1.6)	0.0003
Term	3,993/12,307 (32.4%)	ref	ref

Web Table 3 – Characteristics for the Wheezing-Phenotypes for the Preterm Children Only.

United Kingdom, Year of Birth 2000-2002

	No-Wheeze n = 693	Early-Wheeze n = 189	Persistent-Wheeze n = 137	Late-Wheeze n = 30	All children with positive wheezing phenotype n = 356	*P* value between the four wheezing phenotype groups
Mean birth-weight (kg) (SD)*	2.39 (0.65)	2.18 (0.76)	2.28 (0.69)	2.21 (0.59)	2.22(0.72)	0.00
Mean birth-weight (z-score) (SD)	0.07 (1.20)	-0.17 (1.26)	-0.05 (1.17)	0.05 (1.02)	-0.11 (1.21)	0.09
Mean gestation (weeks) (SD)*	34.52 (2.21)	33.89 (2.90)	34.12 (2.59)	33.84 (2.66)	33.98 (2.76)	0.01
IUGR at birth N (%)	84/692 (12.1)	35/189 (18.5)	23/137 (16.8)	3/30 (10.0)	61/356 (17.1)	0.09
Male N (%)	343/693 (49.5)	95/189 (50.3)	82/137 (59.9)	16/30 (53.3)	193/356 (54.2)	0.17
Antenatal maternal smoking N (%) *	248/691 (35.9)	86/189 (45.5)	60/137 (43.8)	14/30 (46.7)	160/356 (44.9)	0.04
Antenatal smoke exposure N(%)*						0.03
none	443/691 (64.1)	103/189 (54.5)	77/137 (56.2)	16/30 (53.3)	196/356 (55.1)	
1-9 cigarette	74/691 (10.7)	16/189 (8.5)	15/137 (10.9)	1/30 (3.3)	32/356 (9.0)	
10-19 cigarette	95/691 (13.7)	44/189 (23.3)	26/137 (19.0)	6/30 (20.0)	76/356 (21.3)	
>/= 20 cigarette	79/691 (11.4)	26/189 (13.8)	19/137 (13.9)	7/30 (23.3)	52/356 (14.6)	
Socio-economic status N (%)						0.50
Management/Professional	193/624 (30.9)	54/171 (31.6)	45/123 (36.6)	7/27 (25.9)	106/321 (33.0)	
Intermediate	131/624 (21.0)	28/171 (16.4)	13/123 (10.6)	6/27 (22.2)	47/321 (14.6)	
Self employed	25/624 (4.0)	8/171 (4.7)	3/123 (2.4)	2/27 (7.4)	13/321 (4.0)	
Supervisory/Technical	34/624 (5.4)	12/171 (7.0)	8/123 (6.5)	1/27 (3.7)	21/321 (6.5)	
Semi routine/routine	241/624 (38.6)	69/171 (40.4)	54/123 (43.9)	11/27 (40.7)	134/321 (41.7)	
Breast-fed N (%)	465/693 (67.1)	112/189 (59.3)	89/137 (65.0)	22/30 (73.3)	223/356 (62.6)	0.18
Ethnicity white N (%)	574/692 (82.9)	162/189 (85.7)	119/137 (86.9)	26/30 (86.7)	307/356 (86.2)	0.58
Caesarean section N (%)	290/693 (41.8)	93/188 (49.5)	62/137 (45.3)	13/30 (43.3)	168/355 (47.3)	0.30
Admitted to NNU N (%)*	337/693 (48.6)	107/189 (56.6)	80/137 (58.4)	17/29 (58.6)	204/355 (57.5)	0.00

Length of stay after birth (days) (SD) *	15.54 (21.41)	22.50 (29.61)	20.83 (28.35)	20.60 (25.34)	21.70 (28.73)	0.00
Exposure to smoking after birth N (%)	197/693 (28.4)	60/189 (31.7)	48/137 (35.0)	12/30 (40.0)	120/356 (33.7)	0.25
Asthma-diagnosis N (%)*	111/693 (16.0)	91/189 (48.1)	124/137 (90.5)	13/30 (43.3)	228/356 (64.0)	0.00
Atopy at any age N (%)*	377/693 (54.4)	110/189 (58.2)	112/137 (81.8)	24/30 (80.0)	246/356 (69.1)	0.00
Maternal age at child's birth (yrs) (SD)	28.93 (5.93)	29.75 (6.60)	28.77 (6.43)	29.27 (6.88)	29.33 (6.56)	0.39
Maternal history of atopy N (%)*						0.01
Missing	1/693 (0.0)	0/189 (0.0)	0/137 (0.0)	0/30 (0.0)	0/356 (0.0)	
Asthma and Eczema	38/693 (5.5)	12/189 (6.3)	19/137 (13.9)	4/30 (13.3)	35/356 (9.8)	
Asthma or Eczema	157/693 (22.7)	43/189 (22.8)	38/137 (27.7)	5/30 (16.7)	86/356 (24.2)	
None	497/693 (71.7)	134/189 (70.9)	80/137 (58.4)	21/30 (70.0	235/356 (66.0)	
Maternal's BMI before pregnancy (kg/m²) (SD)	23.56 (4.87)	24.25 (6.07)	23.98 (5.68)	23.16 (5.08)	24.06 (5.84)	0.39
Maternal BMI group before pregnancy N (%)						0.17
Not applicable	66/693 (9.5)	11/189 (5.8)	9/137 (6.6)	5/30 (16.7)	25/356 (7.0)	
Underweight	45/693 (6.5)	18/189 (9.5)	9/137 (6.6)	2/30 (6.7)	29/356 (8.1)	
Normal weight	414/693 (59.7)	99/189 (52.4)	82/137 (59.9)	18/30 (60.0)	199/356 (55.9)	
Overweight	101/693 (14.6)	42/189 (22.2)	21/137 (15.3)	1/30 (3.3)	64/356 (18.0)	
Obese	59/693 (8.5)	15/189 (7.9)	14/137 (10.2)	4/30 (13.3)	33/356 (9.3)	
Morbidly Obese	8/693 (1.2)	4/189 (2.1)	2/137 (1.5)	0/30 (0.0)	6/355 (1.7)	
Damp or condensation exposure N(%)	80/693 (11.5)	21/189 (11.1)	21/137 (15.3)	4/30 (13.3)	46/356 (12.9)	0.62
Pollution, grime and environmental problems N (%)						0.45
Very common	47/685 (6.9)	9/188 (4.8)	10/136 (7.4)	4/29 (13.8)	23/353 (6.5)	
Fairly common	91/685 (13.3)	36/188 (19.1)	19/136 (14.0)	4/29 (13.8)	59/353 (16.7)	
Not very common	278/685 (40.6)	66/188 (35.1)	49/136 (36.0)	10/39 (34.5)	125/353 (35.4)	

Not at all common	269/685 (39.3)	77/188 (41.0)	58/136 (42.6)	11/39 (37.9)	146/353 (41.4)	
Number of siblings in household mean mean (SD)	0.83 (1.03)	0.89 (1.18)	0.93 (1.10)	0.93 (1.02)	0.91 (1.13)	0.69
Childcare N(%)						0.81
Formal	85/690 (12.3)	30/187 (16.0)	16/136 (11.8)	4/30 (13.3)	50/353 (14.2)	
Informal	190/690 (27.5)	52/187 (27.8)	35/136 (25.7)	7/30 (23.3)	94/353 (26.6)	

IUGR=intrauterine growth restriction

*** *P* <0.05 between the four wheezing-phenotype groups**

There is missing data for some of the demographics

Web Material

Comparison of the Associations of Early Life Factors on Wheezing-Phenotypes in Preterm-Born Children and Term-Born Children

Sarah J Kotecha, W John Watkins, John Lowe, Raquel Granell, A John Henderson, and Sailesh Kotecha.

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Web Appendix 1

METHODS

MCS is a cohort of 19,517 children born in the UK between 2000-2002. The children were selected through the Child Benefit system with over-sampling from Wales, Scotland and Northern Ireland. Oversampling also occurred from areas with higher concentrations of Black and Asian families, and from deprived areas.

All data were collected at face-to-face interviews. At nine months of age, data were collected on pregnancy, birth and early life including breast feeding (breast milk intake for any period of time), any antenatal maternal smoking and socio-economic status (based on main carer's last known job), delivery by caesarean section (CS), exposure to damp or condensation, exposure to pollution, grime and environmental problems, number of siblings, childcare use (informal e.g. family members and formal e.g. childminder, nursery etc.), maternal history of atopy (none, asthma and eczema, asthma or eczema), maternal pre-pregnancy body mass index (BMI) (underweight, normal, overweight, obese, morbidly obese), maternal age at birth of child. At 3, 5, 7 and 11 years of age, longitudinal data were collected for respiratory symptoms (including wheeze ever and recent wheeze – defined as parental reporting of wheezing or whistling in the chest – in the last 12 months), asthma-diagnosis (based on parental reports) and child's atopic diseases (diagnosis of eczema and hay fever), exposure to smoking (positive if exposure occurred at any time-point in the same room as the child). Ethnicity was coded as Caucasian or non-Caucasian.

Statistical Analysis

We, used LatentGOLD 5.1 (Statistical Innovations, Boston, Ma., USA) to define the optimal number of phenotypes to study. Children reporting recent-wheeze for at least three time-points were assigned a 4-digit string with the digits assigned 1 or 0 for recent-wheeze at 3, 5, 7 and 11 years. Thus "0000" signified never wheezed and "1111" signified wheezing at all-time points. Where there were three reports of recent-wheeze, the missing time period was assigned an "asterisk". For the term and preterm-born children who had data available at 3 or 4 time points 4 classes were chosen as the first non-significant p-value and the lowest BIC. The class posterior probability was used to assign each wheezing pattern to the class of wheezing-phenotype which they had the highest probability of belonging to. The machine driven approach was used for all the wheezing patterns.

Web Appendix 2

RESULTS

Web Table 1

Web Table 1 compares children who were or were not included. A greater percentage of preterm- and term-born children for whom wheezing data were not available were male, from lower socio-economic classes, had lower rates of breast-fed or asthma-diagnosis, less exposure to post-natal smoking, had younger mothers, a greater percentage of maternal BMIs were outside the normal weight range, were more likely to be from an ethnic minority, were more likely to be exposed to pollution, grime and environmental problems, had lower rates of being in formal or informal childcare but were less likely to be atopic. The term-born children not included also had lower birth-weight z-score and higher exposure to antenatal maternal smoking and had more siblings in the household.

Web Tables

Web Table 1 – Demographics of the Preterm- and Term-Born Children With and Without Wheezing-Phenotype Data. United Kingdom, Year of Birth 2000-2002

	Term children with wheezing phenotype data	Term children without wheezing phenotype data	Preterm children with wheezing phenotype data	Preterm children without wheezing phenotype data
Number	12,307	4,756	1,049	453
Mean birth-weight (kg) (SD)$	3.43 (0.51)	3.39 (0.51)	2.33 (0.68)	2.35 (0.72)
Mean birth-weight (z-score) (SD)$	-0.03 (1.00)	-0.08 (1.01)	0.01 (1.20)	0.04 (1.23)
Mean gestation (weeks) (SD)$	39.81 (1.27)	39.72 (1.29)	34.34 (2.43)	34.18 (2.68)
IUGR at birth N (%)	1,238/12,300 (10.1)	517/4,750 (10.9)	145/1,048 (13.8)	58/453 (12.8)
Male N (%) $*	6,202/12,307 (50.4)	2,501/4,756 (52.6)	536/1,049 (51.1)	268/453 (59.2)
Antenatal maternal smoking N (%)$	3,980/12,291(32.4)	1,892/4,748 (39.8)	408/1,047 (39.0)	181/452 (40.0)
Antenatal smoke exposure N (%)$				
none	8,311/12,291 (67.6)	2,856/4,748 (60.2)	639/1,047 (61.0)	271/452 (60.0)
1-9 cigarette	1,041/12,291 (8.5)	525/4,748 (11.1)	106/1,047 (10.1)	46/452 (10.2)
10-19 cigarette	1,725/12,291 (14.0)	816/4,748 (17.2)	171/1,047 (16.3)	69/452 (15.3)
>/= 20 cigarette	1,214/12,291 (9.9)	551/4,748 (11.6)	131/1,047 (12.5)	66/452 (14.6)
Socio-economic status N (%)$*				
Management/Professional	3,655/11,109 (32.9)	841/3,997 (21.0)	299/945 (31.6)	89/389 (22.9)
Intermediate	2,148/11,109 (19.3)	733/3,997 (18.3)	178/945 (18.8)	69/389 (17.7)
Self employed	464/11,109 (4.2)	142/3,997 (3.6)	38/945 (4.0)	7/389 (1.8)
Supervisory/Technical	663/11,109 (6.0)	252/3,997 (6.3)	55/945 (5.8)	25/389 (6.4)
Semi routine/routine	4,179/11,109 (37.6)	2,029/3,997 (50.8)	375/945 (39.7)	199/389 (51.2)
Breast fed N (%) $*	8,493/12,306 (69.0)	2,740/4,753 (57.6)	688/1,049 (65.6)	267/453 (58.9)
Ethnicity white N (%) $*	10,416/12,284 (84.8)	3,724/4,751 (78.4)	881/1,048 (84.1)	353/453 (77.9)
Caesarean section N (%)	2,516/12,252 (20.5)	1,000/4,739 (21.1)	458/1,048 (43.7)	194/453 (42.8)
Admitted to NNU N (%)$	710/12,307 (5.8)	297/4,751 (6.3)	541/1,048 (51.6)	223/453 (49.2)
Length of stay after birth (days) (SD)*	3.12 (5.81)	3.25 (6.09)	17.63 (24.31)	21.45 (34.91)
Exposure to smoking after birth N (%)$*	3,436/12,307 (27.9)	1,090/4,755 (22.9)	317/1,049 (30.2)	103/452 (22.8)
Atopy at any age N (%)$*	7,377/12,307 (59.9)	1,253/2,978 (42.1)	623/1,049 (59.4)	116/291 (39.9)
Asthma-diagnosis N (%)$*	2,969/12,307 (24.1)	527/2,973 (17.7)	339/1,049 (32.3)	69/291 (23.7)
Maternal age at child's birth (yrs) (SD) *$	28.8 (5.8)	27.2 (6.1)	29.1 (6.1)	27.3 (6.4)
Maternal history of atopy N (%)				
Missing	9/12,307 (0.0)	1/4,756 (0.0)	1/1,049 (0.0)	0/453 (0)
Asthma and Eczema	697/12,307 (5.7)	264/4,756 (5.6)	73/1,049 (7.0)	28/453 (6.2)
Asthma or Eczema	2,716/12,307 (22.1)	980/4,756 (20.6)	243/1,049 (23.2)	83/453 (18.3)
None	8,885/12,307 (72.2)	3,511/4,756 (73.8)	732/1,049 (69.8)	342/453 (75.5)
Maternal's BMI before child's pregnancy (kg/m^2) (SD) *$	23.8 (4.4)	23.4 (4.3)	23.7 (5.2)	23.1 (4.9)
Maternal BMI group before pregnancy N (%)*$				
Refusal	2/12,307 (0)	2/4,756 (0)	0/1,049 (0)	0/453 (0)
Not applicable	960/12,307 (7.8)	480/4,756 (10.1)	91/1,049 (8.7)	51/453 (11.3)

Underweight	593/12,307 (4.8)	307/4,756 (6.5)	74/1,049 (7.1)	44/453 (9.7)
Normal weight	7,396/12,307 (60.1)	2,798/4,756 (58.8)	613/1,049 (58.4)	252/453 (55.6)
Overweight	2,368/12,307 (19.2)	809/4,756 (17.0)	165/1,049 (15.7)	78/453 (17.2)
Obese	906/12,307 (7.4)	338/4,756 (7.1)	92/1,049 (8.8)	22/543 (4.9)
Morbidly Obese	82/12,307 (0.7)	22/4,756 (0.5)	14/1,049 (1.3)	6/453 (1.3)
Damp or condensation exposure N (%)	1,654/12,285 (13.5)	682/4,738 (14.4)	126/1,049 (12.0)	69/452 (15.3)
Pollution, grime and environmental problems N (%)*$				
Very common	749/12,183 (6.1)	320/4,685 (6.8)	70/1,038 (6.7)	39/449 (8.7)
Fairly common	1,943/12,183 (15.9)	818/4,685 (17.5)	150/1,038 (14.5)	72/449 (16.0)
Not very common	4,773/12,183 (39.2)	1,789/4,685 (38.2)	403/1,038 (38.3)	195/449 (43.4)
Not at all common	4,718/12,183 (38.7)	1,758/4,685 (37.5)	415/1,038 (40.0)	143/449 (31.8)
Number of siblings in household N$	0.93 (1.0)	0.97 (1.1)	0.86 (1.1)	0.87 (1.1)
Childcare N (%)*$				
Formal	1,758/12,276 (14.3)	376/4,749 (8.0)	135/1,043 (12.9)	35/451 (7.8)
Informal	3,882/12,276 (31.6)	1,248/4,749 (26.3)	284/1,043 (27.2)	105/451 (23.3)

IUGR= intrauterine growth restriction
$ ***P*** <0.05 between those with and without wheezing-phenotype data for the term children
* ***P*** <0.05 between those with and without wheezing-phenotype data for the preterm children

Web Table 2 – Unadjusted Odds Ratio of Recent Wheeze at Each Age for Each Gestation Band Against Term. United Kingdom, Year of Birth 2000-2002.

Gestation group	3 years of age (N)	Odds ratio (95% CI)	*P* -value
24-32 weeks	62/181 (34.3%)	2.2 (1.6, 3.0)	<0.0001
33-34 weeks	62/233 (26.6%)	1.5 (1.1, 2.0)	0.0051
35-36 weeks	135/570 (23.7%)	1.3 (1.1, 1.6)	0.0089
Term	2,228/11,584 (19.2%)	ref	Ref

Gestation group	**5 years of age (N)**	**Odds ratio (95% CI)**	***P* -value**
24-32 weeks	47/186 (25.3%)	1.8 (1.3, 2.5)	0.0006
33-34 weeks	58/240 (24.2%)	1.7 (1.3, 2.3)	0.0006
35-36 weeks	127/596 (21.3%)	1.4 (1.2, 1.8)	0.0005
Term	1,907/12,003 (15.9%)	ref	ref

Gestation group	**7 years of age (N)**	**Odds ratio (95% CI)**	***P* -value**
24-32 weeks	36/178 (20.2%)	1.9 (1.3, 2.7)	0.0009
33-34 weeks	31/232 (13.4%)	1.1 (0.8, 1.7)	0.51
35-36 weeks	83/580 (14.3%)	1.2 (1.0, 1.6)	0.09
Term	1,402/11,743 (11.9%)	ref	Ref

Gestation group	**11 years of age (N)**	**Odds ratio (95% CI)**	***P* -value**
24-32 weeks	33/177 (18.6%)	1.7 (1.2,2.5)	0.006
33-34 weeks	31/221 (14.0%)	1.2 (0.8,1.8)	0.32
35-36 weeks	67/547 (12.2%)	1.0 (0.8, 1.4)	0.76
Term	1,314/11,117 (11.8%)	ref	Ref

Gestation group	**Any wheeze at any time point (N)**	**Odds ratio (95% CI)**	**p-value**
24-32 weeks	101/192 (52.6%)	2.3 (1.7, 3.1)	<0.0001
33-34 weeks	102/249 (41.0%)	1.4 (1.2, 1.9)	0.0047
35-36 weeks	240/608 (39.5%)	1.4 (1.1, 1.6)	0.0003
Term	3,993/12,307 (32.4%)	ref	ref

Web Table 3 – Characteristics for the Wheezing-Phenotypes for the Preterm Children Only. United Kingdom, Year of Birth 2000-2002

	No-Wheeze n = 693	Early-Wheeze n = 189	Persistent-Wheeze n = 137	Late-Wheeze n = 30	All children with positive wheezing phenotype n = 356	*P* value between the four wheezing phenotype groups
Mean birth-weight (kg) (SD)*	2.39 (0.65)	2.18 (0.76)	2.28 (0.69)	2.21 (0.59)	2.22(0.72)	0.00
Mean birth-weight (z-score) (SD)	0.07 (1.20)	-0.17 (1.26)	-0.05 (1.17)	0.05 (1.02)	-0.11 (1.21)	0.09
Mean gestation (weeks) (SD)*	34.52 (2.21)	33.89 (2.90)	34.12 (2.59)	33.84 (2.66)	33.98 (2.76)	0.01
IUGR at birth N (%)	84/692 (12.1)	35/189 (18.5)	23/137 (16.8)	3/30 (10.0)	61/356 (17.1)	0.09
Male N (%)	343/693 (49.5)	95/189 (50.3)	82/137 (59.9)	16/30 (53.3)	193/356 (54.2)	0.17
Antenatal maternal smoking N (%) *	248/691 (35.9)	86/189 (45.5)	60/137 (43.8)	14/30 (46.7)	160/356 (44.9)	0.04
Antenatal smoke exposure N(%)*						0.03
none	443/691 (64.1)	103/189 (54.5)	77/137 (56.2)	16/30 (53.3)	196/356 (55.1)	
1-9 cigarette	74/691 (10.7)	16/189 (8.5)	15/137 (10.9)	1/30 (3.3)	32/356 (9.0)	
10-19 cigarette	95/691 (13.7)	44/189 (23.3)	26/137 (19.0)	6/30 (20.0)	76/356 (21.3)	
>/= 20 cigarette	79/691 (11.4)	26/189 (13.8)	19/137 (13.9)	7/30 (23.3)	52/356 (14.6)	
Socio-economic status N (%)						0.50
Management/Professional	193/624 (30.9)	54/171 (31.6)	45/123 (36.6)	7/27 (25.9)	106/321 (33.0)	
Intermediate	131/624 (21.0)	28/171 (16.4)	13/123 (10.6)	6/27 (22.2)	47/321 (14.6)	
Self employed	25/624 (4.0)	8/171 (4.7)	3/123 (2.4)	2/27 (7.4)	13/321 (4.0)	
Supervisory/Technical	34/624 (5.4)	12/171 (7.0)	8/123 (6.5)	1/27 (3.7)	21/321 (6.5)	
Semi routine/routine	241/624 (38.6)	69/171 (40.4)	54/123 (43.9)	11/27 (40.7)	134/321 (41.7)	
Breast-fed N (%)	465/693 (67.1)	112/189 (59.3)	89/137 (65.0)	22/30 (73.3)	223/356 (62.6)	0.18
Ethnicity white N (%)	574/692 (82.9)	162/189 (85.7)	119/137 (86.9)	26/30 (86.7)	307/356 (86.2)	0.58
Caesarean section N (%)	290/693 (41.8)	93/188 (49.5)	62/137 (45.3)	13/30 (43.3)	168/355 (47.3)	0.30

Admitted to NNU N (%)*	337/693 (48.6)	107/189 (56.6)	80/137 (58.4)	17/29 (58.6)	204/355 (57.5)	0.00
Length of stay after birth (days) (SD) *	15.54 (21.41)	22.50 (29.61)	20.83 (28.35)	20.60 (25.34)	21.70 (28.73)	0.00
Exposure to smoking after birth N (%)	197/693 (28.4)	60/189 (31.7)	48/137 (35.0)	12/30 (40.0)	120/356 (33.7)	0.25
Asthma-diagnosis N (%)*	111/693 (16.0)	91/189 (48.1)	124/137 (90.5)	13/30 (43.3)	228/356 (64.0)	0.00
Atopy at any age N (%)*	377/693 (54.4)	110/189 (58.2)	112/137 (81.8)	24/30 (80.0)	246/356 (69.1)	0.00
Maternal age at child's birth (yrs) (SD)	28.93 (5.93)	29.75 (6.60)	28.77 (6.43)	29.27 (6.88)	29.33 (6.56)	0.39
Maternal history of atopy N (%)*						0.01
Missing	1/693 (0.0)	0/189 (0.0)	0/137 (0.0)	0/30 (0.0)	0/356 (0.0)	
Asthma and Eczema	38/693 (5.5)	12/189 (6.3)	19/137 (13.9)	4/30 (13.3)	35/356 (9.8)	
Asthma or Eczema	157/693 (22.7)	43/189 (22.8)	38/137 (27.7)	5/30 (16.7)	86/356 (24.2)	
None	497/693 (71.7)	134/189 (70.9)	80/137 (58.4)	21/30 (70.0	235/356 (66.0)	
Maternal's BMI before pregnancy (kg/m^2) (SD)	23.56 (4.87)	24.25 (6.07)	23.98 (5.68)	23.16 (5.08)	24.06 (5.84)	0.39
Maternal BMI group before pregnancy N (%)						0.17
Not applicable	66/693 (9.5)	11/189 (5.8)	9/137 (6.6)	5/30 (16.7)	25/356 (7.0)	
Underweight	45/693 (6.5)	18/189 (9.5)	9/137 (6.6)	2/30 (6.7)	29/356 (8.1)	
Normal weight	414/693 (59.7)	99/189 (52.4)	82/137 (59.9)	18/30 (60.0)	199/356 (55.9)	
Overweight	101/693 (14.6)	42/189 (22.2)	21/137 (15.3)	1/30 (3.3)	64/356 (18.0)	
Obese	59/693 (8.5)	15/189 (7.9)	14/137 (10.2)	4/30 (13.3)	33/356 (9.3)	
Morbidly Obese	8/693 (1.2)	4/189 (2.1)	2/137 (1.5)	0/30 (0.0)	6/355 (1.7)	
Damp or condensation exposure N(%)	80/693 (11.5)	21/189 (11.1)	21/137 (15.3)	4/30 (13.3)	46/356 (12.9)	0.62
Pollution, grime and environmental problems N (%)						0.45
Very common	47/685 (6.9)	9/188 (4.8)	10/136 (7.4)	4/29 (13.8)	23/353 (6.5)	
Fairly common	91/685 (13.3)	36/188 (19.1)	19/136 (14.0)	4/29 (13.8)	59/353 (16.7)	

Not very common	278/685 (40.6)	66/188 (35.1)	49/136 (36.0)	10/39 (34.5)	125/353 (35.4)	
Not at all common	269/685 (39.3)	77/188 (41.0)	58/136 (42.6)	11/39 (37.9)	146/353 (41.4)	
Number of siblings in household mean mean (SD)	0.83 (1.03)	0.89 (1.18)	0.93 (1.10)	0.93 (1.02)	0.91 (1.13)	0.69
Childcare N(%)						0.81
Formal	85/690 (12.3)	30/187 (16.0)	16/136 (11.8)	4/30 (13.3)	50/353 (14.2)	
Informal	190/690 (27.5)	52/187 (27.8)	35/136 (25.7)	7/30 (23.3)	94/353 (26.6)	

IUGR=intrauterine growth restriction

*** *P* <0.05 between the four wheezing-phenotype groups**

There is missing data for some of the demographics

Web Figure 1 - Assumed Causal Pathway Linking Early Life Factors and Characteristics to Preterm Birth and/or Later Wheezing. United Kingdom, Year of Birth 2000-2002.