OPEN ACCESS

University of BRISTOL

University of Bristol - Explore Bristol Research
General rights

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.

Table of contents

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 cigarettes	1,041/12,291 (8.5)	525/4,748 (11.1)	106/1,047 (10.1)	46/452 (10.2)
10-19 cigarettes	1,725/12,291 (14.0)	816/4,748 (17.2)	171/1,047 (16.3)	69/452 (15.3)
>/= 20 cigarettes	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/m²) (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

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)

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.