

ONLINE DATA SUPPLEMENT

Title:

What does adolescent undiagnosed-wheeze represent? Findings from the Isle of Wight Cohort

Authors:

*Abid Raza , Clinical Research Fellow

*Ramesh J Kurukulaaratchy, Consultant Respiratory Physician

Jane Grundy, Research Nurse

Bernie Clayton, Research Nurse

Frances Mitchell, Research Nurse

Graham Roberts, Professor

Susan Ewart Professor

S Hasan Arshad, Professor

* AR& RJK contributed equally to this manuscript

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Additional Details of Statistical Methods:

Socio-Economic Class assessment:

Standard Occupational Classification [E1] and UK National Statistics Socio-economic Classification (NS-SEC) [E2] were applied at 10 and 18-years respectively. Six categories of social class were reduced to 2 analytic groups; social classes I-III NM (High), III M-V (Low).

Analysis of Urinary Cotinine Data:

Continuous data on urinary cotinine was transformed into categorical form using an optimal binning method [E3] with current tobacco smoking as the optimizing variable. Three categories (low, moderate, high) were identified.

References:

- E1. Office of population censuses and surveys. Standard Occupational Classification 1991; Vol 1-3.
- E2. The National Statistics Socio-economic Classification Manual. 2005. p. 1-99.
- E3. Fayyad, U, Irani, K. Multi-interval discretization of continuous-value attributes for classification learning. In: *Proceedings of the Thirteenth International Joint Conference on Artificial Intelligence*. 1993. San Mateo, CA: Morgan Kaufmann.

Table E1: Comparison of Healthcare use between Undiagnosed-wheeze and Asthma

	Undiagnosed-Wheeze	Asthma
Hospital visits	2% (1/56)	7% (15/226)
p -value		0.21
A&E attendance	4% (2/56)	12% (26/226)
p -value		0.08
Missed School	9% (4/44)	18% (37/201)
p -value		0.18

Table E1 Notes: Fisher Exact Test used for comparison between undiagnosed-wheeze and Asthma with significance determined at <0.05

Table E2: Gender difference assessed for difference in BHR

BHR	Overall	Never asthma	Non-wheeze	Undiagnosed-wheeze	Asthma
10 year					
Male (n)	1.48 (362)	1.32 (206)	1.36 (266)	1.38 (17)	1.94 (79)
Female (n)	1.45 (361)	1.33 (212)	1.36 (248)	1.38 (21)	1.73 (92)
p-value	0.40	0.75	0.96	0.94	0.03
18 year					
Male (n)	1.12 (292)	1.05 (181)	1.05 (222)	1.13 (13)	1.36 (57)
Female(n)	1.14 (293)	1.08 (197)	1.08 (225)	1.03 (12)	1.37 (56)
p-value	0.41	0.27	0.16	0.40	0.85

Table E2 Notes:

Independent samples t-test was applied with significance determined at $p < 0.05$

(n) represents number of participants in each group

Table E3: Cross-sectional lung function, height and BHR analysis at 10 and 18-yrs for wheeze phenotypes

10 Year	Lung Function/BHR	B	95% CI	p-value
Asthma*	FEV1	- 0.04	-0.10 - 0.02	0.15
	FVC	0.03	-0.03 - 0.09	0.34
	FEV1/FVC	- 0.03	-0.04- (-0.02)	<0.001
	FEF25-75%	- 0.27	-0.40 - (-0.13)	<0.001
	DRS [§]	0.48	0.38 - 0.58	<0.001
Undiagnosed Wheeze *	FEV1	- 0.06	-0.15 - 0.04	0.24
	FVC	- 0.05	-0.14 - 0.05	0.35
	FEV1/FVC	- 0.004	-0.03 - 0.02	0.74
	FEF25-75%	- 0.004	-0.22 - 0.22	0.98
	DRS [§]	0.05	- 0.16 - 0.26	0.66
18 year				
Asthma*	FEV1	- 0.25	-0.37 - (-0.13)	<0.001
	FVC	- 0.09	-0.23-0.05	0.20
	FEV1/FVC	- 0.05	-0.06 - (-0.03)	<0.001
	FEF25-75%	- 0.58	-0.83 - (-0.34)	<0.001
	DRS [§]	0.30	0.24 - 0.36	<0.001
	%FEV ₁ Reversibility**	4.35	3.36 - 5.32	<0.001
Undiagnosed Wheeze*	FEV1	- 0.25	-0.45 - (-0.04)	0.03
	FVC	- 0.30	-0.53- (-0.06)	0.02
	FEV1/FVC	0.004	-0.03 - 0.03	0.80
	FEF25-75%	- 0.19	-0.60 - 0.22	0.36

DRS [§]	- 0.03	-0.16 – 0.09	0.61
%FEV ₁	0.004	-1.67 – 1.68	1.00
Reversibility ^{**}			

Table E3 Notes:

Comparison between groups was performed using repeated measures General Linear Models (GLM) adjusted for height and sex with significance at $p < 0.05$.

Number of participants per group Non-wheeze = 521, UDW = 39, Asthma = 139

* Group comparisons of undiagnosed-wheeze and asthma against reference of non-wheeze.

§ BHR DRS: refers to a continuous dose-response (DRS) measure of bronchial hyper-responsiveness (BHR) expressed as $\text{Log}_{10}(\text{DRS} + 10)$; higher values infer greater BHR.

Number of participants for BHR: Non-wheeze = 592, UDW = 45, Asthma = 153

** %FEV₁ reversibility: to 600 micrograms inhaled salbutamol. GLM univariate model applied with significance at $p < 0.05$ for this variable.

Table E4: Univariate analysis of risk factors for undiagnosed-wheeze from birth to 18 years

	Undiagnosed-wheeze % (n/total)	Non-Wheeze % (n/total)	OR	95% Confidence Interval	p - value
Maternal smoking during pregnancy	34 (22/64)	24 (235/994)	1.69	0.99 - 2.89	0.06
Home tobacco smoke exposure during pregnancy *	58 (37/64)	45 (447/999)	1.69	1.02 - 2.82	0.04
Smoke exposure at 1	40 (22/55)	40 (372/934)	1.00	0.58 - 1.76	0.98
Smoke exposure at 2	40 (19/47)	40 (342/840)	0.99	1.00 - 1.80	0.97
Smoke exposure at 4	39 (20/51)	42 (81/192)	1.00	0.56 - 1.78	0.99
Smoke exposure at 10	49 (23/47)	48 (93/194)	1.26	0.70- 2.26	0.45
Home tobacco smoke exposure at 18-years (active and passive)	61 (39/64)	41 (414/1008)	2.24	1.33 - 3.76	0.002
Current and past self-smoke exposure 18-years†	73 (47/64)	45 (437/977)	3.42	1.93 - 6.03	<0.001
Chest infection at 1 year	9 (5/54)	7 (62/926)	1.42	0.55 - 3.70	0.47
Chest infection at 2year	15 (7/47)	12 (99/838)	1.31	0.57 - 3.00	0.53
Lower social class at pregnancy‡	55 (23/42)	54 (321/593)	0.98	0.52 - 1.83	0.94
Lower social class at 10 ‡	58 (29/50)	50 (428/864)	1.41	0.79 - 2.51	0.25
Lower social class at 18 ‡	42 (22/53)	32 (292/909)	1.50	0.85 - 2.64	0.16
Pet cat 0	30 (19/64)	34 (339/1002)	0.83	0.48 - 1.43	0.50
Pet cat 1	24 (13/54)	31 (292/938)	0.70	0.37 - 1.33	0.28
Pet cat 2	76 (35/46)	80 (678/848)	0.80	0.40 - 1.60	0.53
Pet cat 4	35 (18/52)	37 (315/864)	0.92	0.51- 1.66	0.79
Pet cat 10	41 (24/58)	44 (424/959)	0.89	0.52 - 1.53	0.67
Pet cat 18	41 (26/64)	42 (421/999)	0.94	0.56 - 1.57	0.81
Pet dog 0	33 (21/64)	28 (285/1002)	1.23	0.72 - 2.11	0.45
Pet dog 1	28 (15/54)	26 (248/938)	1.07	0.58 - 1.98	0.83
Pet dog 2	24 (11/46)	17 (146/848)	1.51	0.75 - 3.05	0.25
Pet dog 4	29 (15/52)	28 (239/864)	1.06	0.57 - 1.97	0.85
Pet dog 10	45 (26/58)	38 (361/959)	1.35	0.79 - 2.30	0.28
Pet dog 18	56 (36/64)	48 (477/997)	1.40	0.84 - 2.33	0.19
Rhinitis at 1	13 (7/55)	9 (81/938)	1.54	0.68 - 3.52	0.30
Rhinitis at 2	6 (3/49)	10 (83/853)	0.61	0.18 - 1.99	0.41
Rhinitis at 4	10 (5/51)	4 (34/861)	2.64	0.99 - 7.08	0.05
Rhinitis at 10	17 (10/58)	18 (171/955)	0.96	0.47 - 1.93	0.90
Rhinitis at 18	53 (34/64)	28 (278/1006)	2.97	1.78 - 4.94	<0.001
wheeze at 1	14 (7/51)	11 (101/917)	1.52	0.56 - 2.93	0.55
wheeze at 2	18 (9/49)	14 (114/843)	1.44	0.68 - 3.05	0.34
wheeze at 4	14 (7/51)	10 (89/862)	1.38	0.55 - 3.32	0.44
wheeze at 10	5 (3/58)	10 (95/960)	0.50	0.12 - 1.69	0.24
Atopy at 4-years§	25 (10/40)	14 (99/703)	2.03	0.96- 4.29	0.06
Atopy at 10-years§	23 (11/47)	20 (145/731)	1.17	0.61 - 2.49	0.55
Atopy at 18-years§	38 (17/45)	34 (221/643)	1.16	0.62 - 2.16	0.64

Table E4 Notes:

Comparisons between undiagnosed-wheeze and non-wheeze groups were made using logistic regression for single variables. Odds ratios represent probability of demonstrating undiagnosed- wheeze in relation to non-wheezers.

*Tobacco smoke exposure inside the house by either parents or any other family member.

† Past or current tobacco smoking status determined at age 18

‡Low social class is based on Social Occupation Classification categories (IIIM to V)

§ Atopy defined by at least 1 skin test wheal response ≥ 3 mm diameter

Table E5: Univariate Analysis of Risk Factors for Undiagnosed-Wheeze at Single Time Point

Adolescent factors	Undiagnosed-wheeze (n/total)	Non-Wheeze (n/total)	OR	95% Confidence Interval	p - value
Family history of asthma *	61 (36/59)	43 (419/966)	2.04	1.19 - 3.50	0.009
Breast feed > 3 months	43 (23/53)	47 (434/919)	0.86	0.49 - 1.50	0.59
Paracetamol use per month†	1.0 (0,3) (63)	1.0 (0,2) (983)	1.13	1.06 - 1.20	<0.001
NSAID use per month‡	0 (0,1.5) (63)	0 (0,1) (983)	1.07	1.00 - 1.14	0.056
Number of days exercise at 18‡	3.21 (53)	3.08 (746)	0.94	0.84 - 1.04	0.22

Table E5 Notes:

Comparisons between undiagnosed-wheeze and non-wheeze groups were made using logistic regression for single variables. Odds ratios represent probability of demonstrating undiagnosed-wheeze in relation to non-wheezers.

*Parental or sibling history of asthma recorded at birth

† Median (25th, 75th) percentile reported, represents number of times paracetamol or NSAID use/month

‡Geometric mean of the number of days of vigorously exercise per week is done

Table E6: Univariate Analysis of Risk Factors for Asthma from birth to 18 years

	Asthmatic Wheeze % (n/total)	Non-Wheeze % (n/total)	OR	95% Confidence Interval	p- value
Early life factors					
Maternal smoking during pregnancy	22 (51/233)	24 (235/994)	0.91	0.64 - 1.28	0.57
Home tobacco smoke exposure during pregnancy	46 (106/232)	45 (447/999)	1.04	0.78 -1.38	0.79
Smoke exposure at 1	47 (97/208)	40 (372/934)	1.32	0.98 - 1.79	0.07
Smoke exposure at 2	44 (81/185)	41 (342/840)	1.13	0.82 - 1.56	0.44
Smoke exposure at 4	42 (81/192)	39 (339/863)	1.13	0.82 - 1.55	0.46
Smoke exposure at 10	48 (93/194)	43 (372/859)	1.21	0.88 - 1.65	0.24
Home tobacco smoke exposure at 18-years (active and passive)	45 (105/234)	41 (414/1008)	1.17	0.88 - 1.56	0.29
Current or past self-smoke exposure †	54 (120/224)	45 (437/977)	1.43	1.07 - 1.91	0.017
Chest infection at 1 year	9 (19/209)	7 (62/926)	1.39	0.81 - 2.39	0.23
Chest infection at 2year	18 (34/189)	12 (99/838)	1.64	1.07 - 2.51	0.02
Lower Social Class during pregnancy‡	53 (74/141)	54 (321/593)	1.07	0.74 - 1.54	0.73
Lower social class at 10 ‡	51 (98/193)	50 (428/864)	1.05	0.77 - 1.44	0.76
Lower social class at 18 ‡	35 (74/212)	32 (292/909)	1.13	0.83 - 1.55	0.44
Pet cat 0	31 (71/233)	34 (339/1002)	0.86	0.63 - 1.17	0.33
Pet cat 1	28 (58/210)	31 (292/938)	0.84	0.61 - 1.18	0.32
Pet cat 2	80 (151/188)	80 (678/848)	1.02	0.69 - 1.52	0.91
Pet cat 4	38 (74/194)	37 (315/864)	1.08	0.78 - 1.48	0.66
Pet cat 10	49 (108/220)	44 (424/959)	1.22	0.91 - 1.63	0.19
Pet cat 18	50 (115/232)	42 (421/999)	1.35	1.01 - 1.80	0.04
Pet dog 0	29 (68/233)	28 (285/1002)	1.04	0.76 - 1.42	0.82
Pet dog 1	26 (55/210)	26 (248/938)	0.99	0.70 - 1.39	0.94
Pet dog 2	15 (28/188)	17 (146/848)	0.84	0.54 - 1.31	0.44
Pet dog 4	29 (56/194)	28 (239/864)	1.06	0.75 - 1.50	0.74
Pet dog 10	41 (90/220)	38 (361/959)	1.15	0.85 - 1.55	0.37
Pet dog 18	50 (117/233)	48 (477/997)	1.10	0.83 - 1.46	0.51
Rhinitis at 1	10 (22/211)	9 (81/938)	1.23	0.75 - 2.02	0.41
Rhinitis at 2	12 (22/191)	10 (83/853)	1.21	0.73 - 1.99	0.46
Rhinitis at 4	11 (20/191)	4 (34/861)	2.85	1.60 - 5.10	<0.001
Rhinitis at 10	46 (100/216)	18 (171/955)	3.95	2.89 - 5.41	<0.001
Rhinitis at 18	66 (154/233)	28 (278/1006)	5.11	3.77 - 6.92	<0.001
Wheeze at 1	16 (33/206)	11 (101/917)	1.54	1.01 - 2.36	0.047
Wheeze at 2	24 (45/186)	14 (114/843)	2.04	1.38 - 3.01	<0.001
Wheeze at 4	40 (72/190)	10 (89/862)	5.30	3.62 - 7.77	<0.001
Wheeze at10	61 (134/220)	10 (95/960)	14.19	9.92 - 20.32	<0.001
Atopy at 4-years§	43 (68/159)	14 (99/703)	4.56	3.12 - 6.66	<0.001
Atopy at 10-years§	57 (104/184)	20 (145/731)	5.25	3.73 - 7.41	<0.001
Atopy at 18-years§	69 (114/165)	34 (221/643)	4.27	2.95 - 6.17	<0.001

Table E6 Notes:

Comparisons between asthmatic-wheeze and non-wheeze groups were made using logistic regression for single variables. Odds ratios represent probability of demonstrating undiagnosed- wheeze in relation to non-wheezers.

*Tobacco smoke exposure inside the house by either parents or any other family member.

† Past or current tobacco smoking status determined at age 18

‡Low social class is based on Social Occupation Classification categories (IIIM to V)

§ Atopy defined by at least 1 skin test wheal response ≥ 3 mm diameter

Table E7: Univariate Analysis of Risk Factors for Asthmatic-Wheeze at Single Time Point

Adolescent factors	Asthmatic Wheeze % (n/total)	Non-Wheeze % (n/total)	OR	95% Confidence Interval	p- value
Family History of Asthma *	62 (139/226)	43 (419/966)	2.01	1.55 - 2.81	<0.001
Breast feed > 3 months	44 (91/209)	47 (434/919)	0.86	0.64 - 1.17	0.34
Paracetamol use per month [†]	1.0 (0,3) (223)	1.0 (0,2) (983)	1.12	1.06 - 1.17	<0.001
NSAID use per month [†]	0 (0,1) (223)	0 (0,1) (983)	1.02	0.97 - 1.08	0.42
Number of days exercise/week at 18 [‡]	2.7 (175)	3.08 (746)	0.90	0.80 - 1.01	0.07

Table E7 Notes:

Comparisons between asthmatic-wheeze and non-wheeze groups were made using logistic regression for single variables. Odds ratios represent probability of demonstrating asthmatic wheeze in relation to non-wheezers.

*Family history of asthma, determined at birth from parents

[†] Median (25th, 75th) percentile reported, represents number of times paracetamol or NSAID use/month

[‡]Geometric mean of the number of days of vigorously exercise per week

Table E8: Multivariate Analysis of Factors Associated with Undiagnosed-wheeze and Asthma at 18-yrs (when excluding earlier diagnosis of asthma in the reference “non-wheeze” group)

Risk Factor	Odds ratio	95% Confidence Interval	p - value
Undiagnosed-Wheeze:			
Rhinitis at 18 years	2.66	1.30 – 5.44	0.007
Teenage smoking (past or current)*	2.57	1.20 – 5.48	0.015
Paracetamol use at 18 years†	1.10	1.00 – 1.21	0.049
Family history of asthma‡	2.38	1.15 – 4.91	0.019
Asthma:			
Family History of Asthma‡	1.71	1.10 – 2.67	0.018
Atopy at 4 year §	5.18	3.20 – 8.38	<0.001
Rhinitis at 10 years	4.66	2.96 – 7.34	<0.001
Paracetamol use at 18 years†	1.08	1.01 – 1.16	0.019
Early life asthma at 1 or 2	2.09	1.04 – 4.21	0.04

Table E8 Notes: Factors for undiagnosed-wheeze and asthma showing trends for significance at univariate analysis ($p < 0.1$) against non-wheezers (where non-wheezers with past asthma were excluded) were entered en-bloc into separate logistic regression models to identify independent risk factors for each group. Factors entered for undiagnosed-wheeze included female gender, family history of asthma, home tobacco exposure during pregnancy, atopy at 4-years, teenage smoking, paracetamol use at 18-years, NSAID use at 18-years, and rhinitis at 18-years.