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

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ABSTRACT: We sought to characterise adolescent wheeze in the absence of asthma, which we termed ''undiagnosed wheeze''.

The Isle of Wight Birth Cohort (n=1,456) was reviewed at 1, 2, 4, 10 and 18 yrs. Using questionnaire responses, ''asthma'' was defined as ''ever had asthma'' plus either ''wheezing in the last 12 months'' or ''taking asthma treatment in the last 12 months''; ''undiagnosed wheeze'' as ''wheeze in the last 12 months'' but ''no'' to ''ever had asthma''; and remaining subjects termed ''non-wheezers''.

Undiagnosed wheeze (prevalence 4.9%) accounted for 22% of wheezing at 18 yrs. This was largely adolescent-onset with similar symptom frequency and severity to diagnosed asthma. However, undiagnosed wheezers had significantly higher forced expiratory volume in 1 s to forced vital capacity ratio, less bronchodilator reversibility and bronchial hyperresponsiveness, and were less frequently atopic than asthmatics. Undiagnosed wheezers had earlier smoking onset, higher smoking rates and monthly paracetamol use than non-wheezers. Logistic regression identified paracetamol use (OR 1.11, 95% CI 1.01–1.23; p=0.03), smoking at 18 yrs (OR 2.54, 95% CI 1.19–5.41; p=0.02), rhinitis at 18 yrs (OR 2.82, 95% CI 1.38–5.73; p=0.004) and asthmatic family history (OR 2.26, 95% CI 1.10–4.63; p=0.03) as significant independent risk factors for undiagnosed wheeze.

Undiagnosed wheeze is relatively common during adolescence, differs from diagnosed asthma and has strong associations with smoking and paracetamol use. Better recognition of undiagnosed wheeze and assessment of potential relevance to adult health is warranted.

KEYWORDS: Asthma, lung function, paracetamol, smoking, undiagnosed wheeze, wheezing phenotype

There is considerable heterogeneity to wheezing illnesses [1], despite attempts to provide clear definitions for conditions like asthma [2] and chronic obstructive pulmonary disease (COPD) [3]. Asthma is seen throughout life and has been characterised as comprising numerous phenotypes [4–6]. Childhood asthma phenotypes share symptoms of wheeze with other conditions like viral-associated wheeze and bronchiolitis [7]. Similarly, in adulthood, wheezing may indicate nonasthmatic disease, notably COPD. COPD constitutes a growing burden, largely observed in tobacco smokers, but is uncommon before the fourth decade of life [8].

Prospective studies have supported early life origins for childhood and early adult asthma [9–16]. More recently, attention has turned to early life as also being of possible relevance for the development of COPD [9, 17, 18]. However, early childhood may not be the only period of vulnerability where individuals are susceptible to influences that could contribute to chronic adult respiratory diseases like asthma and COPD. In this context, adolescence is a phase of dynamic physiological change with accelerated growth to reach maximal lung function. In addition to physiological changes, adolescents show significant behavioural changes as they progress towards young adulthood. This may include starting smoking,

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potentially laying the foundations for processes that could harm future respiratory health [19]. Genetic susceptibility to impaired antioxidant levels may also be associated with reduced adolescent lung growth [20]. Tobacco smoke, by enhancing lung oxidative stress, and paracetamol, by impairing antioxidant defences [21], could both plausibly increase the risk of airway disease in susceptible individuals, especially if those exposures occur in a vulnerable period such as adolescence.

Several studies have reported substantial prevalence of childhood, adolescent and adult undiagnosed asthma; wheeze in the absence of diagnosed asthma [22–24]. However, we believe that undiagnosed asthma may not be the proper classification for all who wheeze in adolescence but have not been diagnosed with asthma. Characterisation of such adolescent wheezing remains poor and our understanding of what it represents, and how it arises, is limited. We report findings from the longitudinal Isle of Wight Whole Population Birth Cohort where wheezing illness in the absence of asthma diagnosis, termed undiagnosed wheeze, is characterised in comparison to diagnosed asthma and non wheezers at 18 yrs along with relationships to adolescent-specific and early life factors.

METHODS

An unselected whole population birth cohort (n=1,456) was established on the Isle of Wight (UK) in 1989 to study the natural history of asthma. Participants were assessed at 1, 2, 4, 10 and 18 yrs. Methodology used in the first decade of follow-up has been published previously [25–27].

The local research ethics committee (06/Q1701/34) approved follow-up at 18 yrs. Participants gave informed consent and provided information on respiratory, nasal and dermatological symptoms. Study-specific plus International Study of Asthma and Allergies in Childhood (ISAAC) [28] questionnaires were used. Tobacco smoke exposure was further validated by urinary cotinine analysis (n=621) (ELISA, BioTek Instruments Inc., Potton, UK). Paracetamol and non-steroidal anti-inflammatory drug (NSAID) use was self-reported as ''average number of times taken per month during the past year''. Self-perceived health status was recorded by visual analogue scale (VAS) from the European Quality of Life 5-Dimensional tool (EQ-5D) [29].

Participation was in person, by telephone or by post. Participants attending in person also performed spirometry, bronchodilator reversibility (BDR) to 600 μg inhaled salbutamol, fractional exhaled nitric oxide (F_{ENO}) measurement, methacholine challenge test and skin prick test (SPT). Identical methodology, published previously [30], was used for spirometry and challenge testing at 10 and 18 yrs. F_{ENO} (Nioxmino®, Aerocrine AB, Solna, Sweden) and SPT to common food and aeroallergens (ALK-Abello, Horsholm, Denmark) were performed as reported previously [30].

Definitions

Asthma at 18 yrs represented ''ever had asthma'' and either of ''wheezing in the last 12 months'' or ''asthma treatment in the last 12 months''. Undiagnosed wheeze at 18 yrs represented ''wheeze in the last 12 months'' but negative response to ''ever had asthma''. Participants with neither asthma nor undiagnosed wheeze were labelled non-wheezers at 18. Rhinitis was defined by ''have you ever had a problem with sneezing, runny or blocked nose in the absence of cold or flu'' plus ''symptoms in the last 12 months''. Atopy was defined by positive SPT (mean wheal diameter at least 3 mm greater than negative control) to at least one allergen.

Statistical methods

Data were entered onto SPSS (version 18). Categorical variables were assessed by Chi-squared tests. For normally distributed continuous measures independent (unpaired) samples t-tests were applied. For multiple comparisons, one-way ANOVA with Bonferroni correction was used. For non-normally distributed data, Mann–Whitney U-test and Kruskal–Wallis ANOVA were applied. Three categories (low, moderate and high) of urinary cotinine level were defined. General linear models for repeated measures were used to compare height-adjusted lung function differences and bronchial hyperresponsiveness (BHR) between groups.

BHR was defined by methacholine concentration causing a stable 20% fall in forced expiratory volume in 1 s (FEV_1) from the post-saline value, expressed as PC_{20}, with a positive test determined by PC_{20} <8 mg·mL^{-1}. A continuous dose–response slope (DRS) measure of BHR was also estimated by least-squares regression of percentage change in FEV_1 upon cumulative methacholine dose for each child. The DRS obtained was transformed as $\log_{10}$ (DRS+10), to satisfy normality and homoscedasticity, with higher values inferring greater BHR.

At 18 yrs, participants were asked their average monthly use of paracetamol and NSAID during the past 12 months. Since consumption of both paracetamol and NSAIDs was not normally distributed in our population, data on use of these medications are presented as median values with 25th to 75th centiles. Consequently, we also used these continuous variables for both paracetamol and NSAID use in logistic regression models when considering independent risk factor profiles for the wheezing phenotypes.

To identify risk factors for undiagnosed wheeze and asthma, univariate analysis was performed against non-wheezers. To obtain independent effects of risk factors, all factors with trends for univariate significance at $p<0.1$ were entered *en bloc* into logistic regression models.

Other details of statistical analysis, including categories for socioeconomic status and urinary cotinine are provided in online supplementary material.

RESULTS

A high degree (90%; n=1,306) of cohort follow-up was achieved at 18 yrs. Previously published data demonstrated that participants attending the centre for a ''full visit'' (n=864) at 18 yrs did not differ significantly from the overall cohort participation [27].

At 18 yrs, asthma occurred in 17.9% (234/1,306) of study participants, undiagnosed wheeze in 4.9% (64/1,306) and the remainder were non-wheezers. Most asthmatics (71%) recorded wheezing at one or more assessments in the first decade of life, while only 25% of undiagnosed wheeze (same proportion as non-wheezers) reported wheeze at those earlier assessments.

Clinical characteristics

Morbidity was similar for the two wheezing groups with comparable symptom frequency at 18 yrs (fig. 1). Overall, 66%

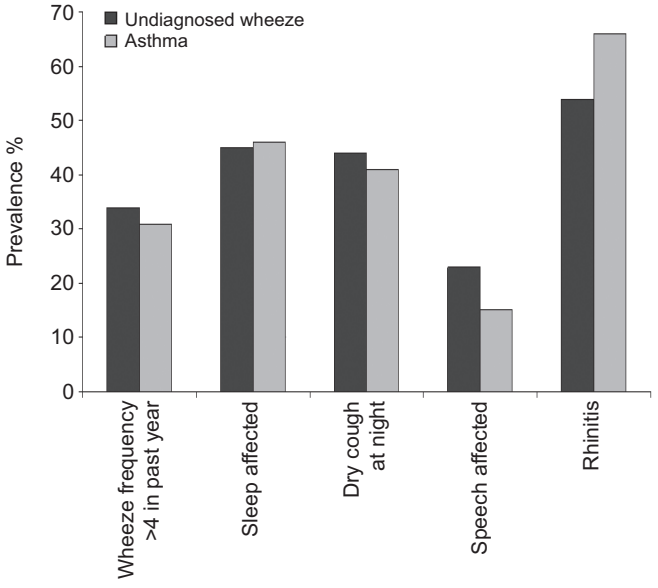

FIGURE 1. Symptom comparison for undiagnosed wheeze and asthma at 18 yrs. Information on symptom prevalence for each group as reported by study participants with minimum n=220 responses for asthmatics and minimum n=63 for undiagnosed wheezers at age 18 yrs. None of the comparisons were statistically significant. Wheeze frequency: four or more episodes in the last year; disturbed sleep: any nocturnal disturbance by wheezing in the last year; nocturnal cough: dry cough at night in the last year (not associated with cold or flu); limited speech: limitation of speech to one or more words at a time by wheeze in the last year; rhinitis: ''sneezing, a runny or blocked nose ever in the absence of cold or flu'' present in the ''last 12 months''.

of asthmatics were taking inhaled corticosteroids compared with none of the undiagnosed wheezers. Wheeze frequency did not differ between asthmatics who were not taking inhaled corticosteroids (32%, 22/68) and undiagnosed wheezers (34%, 22/64; p=0.95). Undiagnosed wheezers had a low self-rated health status (EQ-5D VAS), similar to asthmatics; both groups had significantly lower scores than nonwheezers (p<0.001) (table 1). Healthcare utilisation did not differ significantly between asthmatic and undiagnosed wheezers, although there were trends for greater usage for asthma (online supplementary table E1).

Phenotypic characteristics

Characterisation of wheezing groups (table 1) showed no significant differences in sex, social class, work status or education. Asthma was associated with atopy and significantly higher F_{ENO}, while no difference was observed in atopy or F_{ENO} values between undiagnosed wheeze and non-wheezers. Undiagnosed wheezers and asthmatics both had significantly greater prevalence of asthmatic family history than non-wheezers.

At 10 yrs (table 2), undiagnosed wheezers had normal spirometry, while asthmatics had significantly reduced FEV_1 to forced vital capacity (FVC) ratio and $FEF_{25-75\%}$ (forced expiratory flow at 25–75% of FVC). At 18 yrs, asthmatics still showed evidence of airflow obstruction while undiagnosed wheeze also had lower FEV_1 and FVC (significant for females only) but without significant airflow obstruction. Bronchodilator reversibility at 18 yrs was significantly greater in asthmatics than undiagnosed

TABLE 1 Characteristics of wheeze phenotype at age 18 yrs

	Non-wheeze	Undiagnosed wheeze	Asthma
Demographics			
Female sex	49 (493/1008)	59 (38/64)	55 (128/234)
p-value	Ref.	0.3	0.33
Low social class#	32 (292/909)	42 (22/53)	35 (74/212)
p-value	Ref.	0.48	1
Family history of asthma¶	43 (419/966)	61 (36/59)	62 (139/226)
p-value	Ref.	0.02	<0.001
Still in education at age 18 yrs	71 (699/990)	59 (36/61)	70 (161/230)
p-value	Ref.	0.18	1
In work at age 18 yrs	68 (675/991)	66 (40/61)	69 (158/230)
p-value	Ref.	1	1
Atopy, F_{ENO} and self-rated health status			
Atopy at 18 yrs	34 (221/643)	38 (17/45)	69 (114/165)
p-value	Ref.	1	<0.001
Atopy at 10 yrs	20 (145/731)	23 (11/47)	57 (104/184)
p-value	Ref	1	<0.001
Atopy at 4 yrs	14 (99/703)	25 (10/40)	43 (68/159)
p-value	Ref.	0.18	<0.001
F_{ENO} ppb+ at 18 yrs	17 (425)	18 (24)	31 (107)
p-value	Ref.	1	<0.001
Self-rated health status VAS§	81 (932)	72 (60)	75 (216)
p-value	Ref.	<0.001	<0.001

Data are presented as % (n/N) unless otherwise stated. Comparison of wheeze groups by Chi-squared test for categorical variables determined at p<0.05, group-wise significance adjusted for multiple comparisons. F_{ENO}: exhaled nitric oxide fraction; VAS: visual analogue score. #: low social class categories (IIIM–V); ¶: parent or sibling history of asthma recorded at birth; +: geometric mean (n); §: low scores infer lower self-rated health status (n in parentheses).

wheezers and non-wheezers. Using repeated measures analysis, height- and sex-adjusted adolescent gain in lung function (FEV_1), was significantly lower (p<0.001) for asthmatics with similar trends in undiagnosed wheeze (p=0.07) (table 3 and fig. 2a) when compared to non-wheezers as reference.

Higher prevalence and degree of BHR was observed at both 10- and 18-yr assessments for asthma but not undiagnosed wheezers (table 2). No sex difference in BHR (measured by DRS) was noted (online supplementary table E2) when assessing the overall population, non-wheeze, or undiagnosed wheeze individuals at both 10 and 18 yrs. There was also no gender difference noted for BHR in asthmatics at 18 yrs. Repeated measures analysis for BHR demonstrated an overall decreasing pattern of BHR over the adolescent period (p<0.001) (table 3 and fig. 2b). Asthmatics demonstrated higher BHR compared to non-wheeze at both 10 (p<0.001) and 18 yrs (p<0.001). This was also observed in comparison to undiagnosed wheeze at 10 (p<0.001) and 18 yrs (p<0.001). The asthma group differed significantly from non-wheezers in adolescent lung function changes, showing lower gain in FEV_1 and $FEF_{25-75\%}$, declining FEV_1/FVC ratio and persistently greater BHR as observed in the repeated measures GLM model (table 3). A very different pattern of lung

TABLE 2 Cross-sectional lung function, height and bronchial hyperresponsiveness (BHR) analysis at 10 and 18 yrs for wheeze phenotypes

Lung function	Overall	Non-wheeze	Undiagnosed wheeze	p-value[#]	Asthma	p-value[¶]
18 yrs						
Male n	327	248	16		63	
FEV_1 L	4.62	4.66±0.03	4.54±0.13	0.94	4.43±0.07	0.002
FVC L	5.36	5.34±0.04	5.47±0.15	0.41	5.43±0.08	0.28
FEV_1/FVC	0.86	0.88±0.005	0.86±0.02	0.32	0.82±0.01	<0.001
$FEF_{25-75\%}$ $L \cdot s^{-1}$	4.98	5.14±0.07	5.00±0.28	0.5	4.35±0.14	<0.001
Height cm	178	178	175	0.27	178	1
Female n	372	273	23		76	
FEV_1 L	3.47	3.53±0.02	3.35±0.08	0.027	3.29±0.04	<0.001
FVC L	3.97	4.00±0.03	3.78±0.09	0.024	3.91±0.05	0.14
FEV_1/FVC	0.88	0.89±0.004	0.89 ±0.01	0.9	0.84±0.01	<0.001
$FEF_{25-75\%}$ $L \cdot s^{-1}$	3.95	4.08±0.05	3.93±0.18	0.42	3.48±0.10	<0.001
Height cm	165	165	164	1	164	0.22
All participants n	699	521	39		139	
BHR DRS[+]	1.12 (585)	1.07 (447)	1.08 (25)	1	1.37 (113)	<0.001
% n/N PC_{20}[§]	7.5 (44/585)	3 (12/447)	4 (1/25)	1	27 (31/113)	<0.001
%FEV_1 reversibility n[f]	5 (585)	4.2	4.2	1	8.5	<0.001
10 yrs						
Male n	327	248	16		63	
FEV_1 L	2.07	2.09±0.02	2.06±0.06	0.7	2.01±0.03	0.02
FVC L	2.37	2.36±0.02	2.38±0.06	0.83	2.39±0.03	0.44
FEV_1/FVC	0.88	0.88±0.04	0.87±0.01	0.27	0.84±0.07	<0.001
$FEF_{25-75\%}$ $L \cdot s^{-1}$	2.39	2.45±0.03	2.36±0.13	0.5	2.13±0.07	<0.001
Height cm	139	139	138	0.23	139	0.77
Female n	372	273	23		76	
FEV_1 L	2	2.01±0.01	1.96±0.04	0.21	1.97±0.02	0.13
FVC L	2.25	2.24±0.01	2.20±0.04	0.32	2.27±0.02	0.3
FEV_1/FVC	0.89	0.90±0.003	0.90±0.01	0.74	0.87±0.06	<0.001
$FEF_{25-75\%}$ $L \cdot s^{-1}$	2.48	2.53±0.03	2.53±0.11	0.97	2.27±0.06	<0.001
Height cm	139	139	140	0.77	138	0.13
All participants n	699	521	39		139	
BHR DRS[+]	1.47 (723)	1.36 (515)	1.37 (39)	1	1.84 (169)	<0.001
%PC_{20}[§]	31 (221/725)	22 (111/516)	23 (9/40)	1	60 (101/169)	<0.001

Data are presented as height-adjusted mean±SE, unless otherwise stated. FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; $FEF_{25-75\%}$: forced expiratory flow at 25–75% of FVC; DRS: dose–response slope; PC_{20}: provocative concentration causing a 20% fall in FEV_1. [#]: p-values for comparisons of undiagnosed wheeze against reference of nonwheeze; [¶]: p-values for comparisons of asthma against reference of nonwheeze; [+]: expressed as $\log_{10}$ (DRS+10), higher values refers to greater BHR; [§]: %PC_{20} (n in parentheses): proportion within each group demonstrating BHR at methacholine challenge as defined by PC_{20} <8 $mg \cdot mL^{-1}$; Chi-squared test was used with significance determined at $p<0.05$; [f]: %FEV_1 reversibility to 600 μg inhaled salbutamol (n in parentheses). Comparison between groups was performed using generalised linear models adjusted for height with significance at $p<0.05$.

function was noted for undiagnosed wheezers with only trends of decreasing large airway (FEV_1) function for this group when compared to non-wheezers. There was no difference in results for height- and sex-adjusted data for lung function using GLM repeated measures (online supplementary table E3).

Allergic asthma triggers were reported significantly more for asthma than undiagnosed wheeze (fig. 3). Rhinitis occurred with similarly higher frequency in undiagnosed wheeze (53%, 34/64) and asthma (66%, 154/233) than non-wheeze (28%, 278/1006; $p<0.001$). Atopic rhinitis was significantly commoner in asthmatics (79%, 96/121) than non-wheezers (65%, 123/189; $p=0.01$) with similar non-significant differences against undiagnosed wheeze (58%, 14/24; $p=0.053$).

Risk factors

To further characterise undiagnosed wheeze, we investigated the role of common environmental risk factors (table 4). Major differences between phenotypes were found in exposure to cigarette smoke and paracetamol. Undiagnosed wheeze had significantly greater domestic exposure to smoking during pregnancy than non-wheezers, whereas asthmatics showed no difference (table 4). Significantly more undiagnosed wheezers were smokers at 18 yrs compared to non-wheezers (table 4) and asthmatics ($p=0.029$). Current or past personal smoking was seen in 73% of undiagnosed wheeze with no significant sex difference ($p=1.0$). Current tobacco smoke exposure in undiagnosed wheeze was validated by greater moderate–high

TABLE 3 Longitudinal lung function changes from 10 to 18 yrs for asthma and undiagnosed wheeze

	Lung function/ BHR	B	95% CI	p-value
Asthma#	FEV_1	-0.16	-0.22– -0.10	<0.001
	FVC	0.02	-0.04–0.09	0.51
	FEV_1/FVC	-0.04	-0.05– -0.03	<0.001
	$FEF_{25–75\%}$	-0.49	-0.61– -0.36	<0.001
	DRS¶	0.38	0.30–0.45	<0.001
Undiagnosed# wheeze	FEV_1	-0.10	-0.21–0.08	0.07
	FVC	-0.08	-0.20–0.04	0.18
	FEV_1/FVC	-0.009	-0.03–0.01	0.36
	$FEF_{25–75\%}$	-0.14	-0.37–0.08	0.21
	DRS¶	0.02	-0.12–0.16	0.78

Data are presented as mean change unless otherwise stated. Asthma: n=139; undiagnosed wheeze: n=39; non-wheeze: n=521. B: mean difference for repeated measures; BHR: bronchial hyperresponsiveness; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; $FEF_{25–75\%}$: forced expiratory flow at 25-–75% of FVC; DRS: dose–response slope. #: reference group was non-wheeze group. ¶: a continuous DRS measure of BHR expressed as $\log_{10}$ (DRS+10). Generalised linear model repeated measures analysis where lung function was adjusted for sex and height at 10 yrs and significance determined at p<0.05.

cotinine levels than non-wheezers (table 4) and asthmatics (p=0.002). Undiagnosed wheeze also had earlier smoking onset than non-wheezers (table 4) and asthmatics (p=0.016). Furthermore, smoking onset preceded wheeze onset significantly more often in undiagnosed wheezers than in asthmatics (fig. 4). Undiagnosed wheeze reported higher paracetamol and NSAID use per month than non-wheezers, with similar consumption to asthmatics. Overall, females reported higher consumption of both paracetamol and NSAIDs (p<0.001). After sex stratification we observed that male undiagnosed wheezers had significantly higher NSAID intake than male non-wheezers. Female undiagnosed wheezers had significantly higher paracetamol intake than female non-wheezers. This sex-related pattern differed from asthmatics where males and females demonstrated higher paracetamol (rather than NSAID) use than non-wheezers.

Longitudinal data on multiple variables collected from birth (online supplementary tables E4 and E6) plus factors gathered at single time points (online supplementary tables E5 and E7) showing univariate significance for undiagnosed wheeze and for asthma are presented in an online data supplement. In a multivariate logistic regression model controlling for sex, independent significance for developing undiagnosed wheeze was found for rhinitis at 18 yrs, asthmatic family history, paracetamol use and current smoking (table 5). Similar multiple logistic regression analysis for asthma identified independent significance for rhinitis at 10 yrs, asthmatic family history and paracetamol use but instead of smoking, it had atopy at 18 yrs as a significant factor (table 5). Exclusion of former asthmatics from the non-wheeze group did not alter the results of these regression analyses (online supplementary table E8).

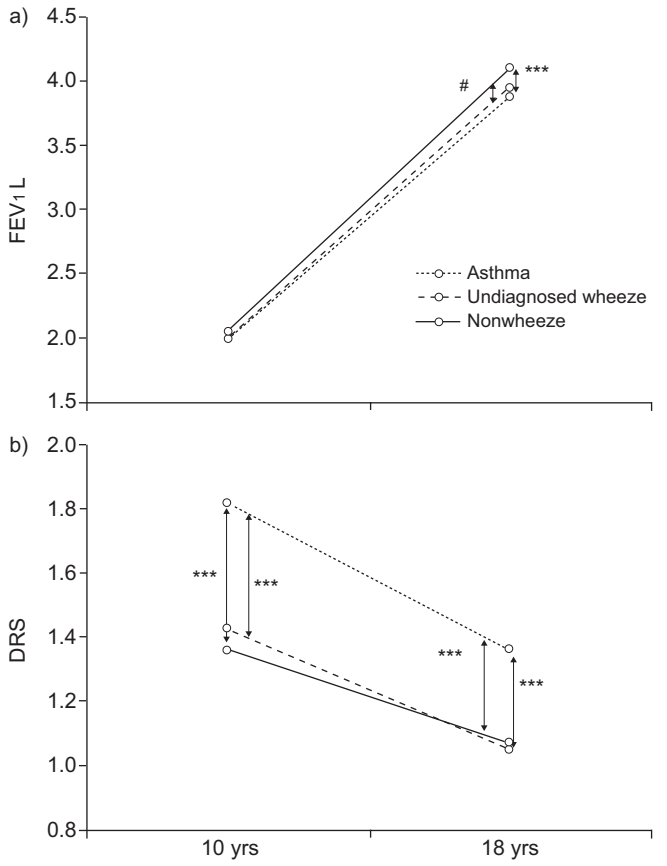

FIGURE 2. a) Longitudinal analysis of lung function (forced expiratory volume in 1 s; FEV_1) from 10 to 18 yrs for wheeze groups. Generalised linear model (GLM) repeated measures analysis with significance at p<0.05. Estimated marginal means of lung function (FEV_1) change over 10–18 yrs was controlled for height at baseline at 10 yrs of age and sex. b) Longitudinal analysis of bronchial hyperresponsiveness from 10 to 18 yrs for wheeze groups. GLM repeated measures analysis with significance at p<0.05. DRS: dose–response slope (estimated marginal means). ***: p<0.001; #: p=0.03.

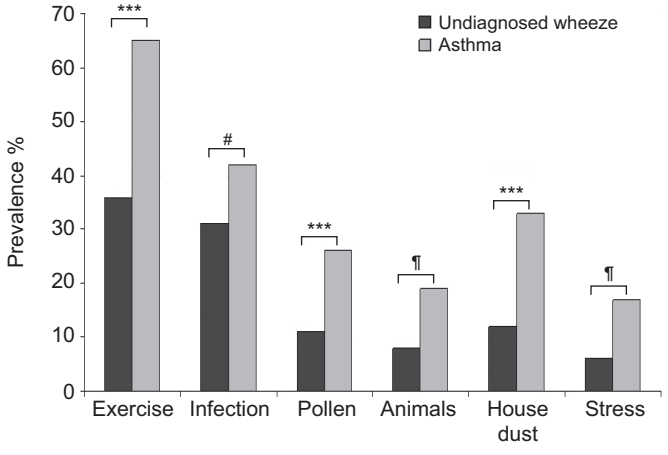

FIGURE 3. Triggers for asthma and undiagnosed wheeze at 18 yrs. Information on percentage of trigger for wheeze in each group as reported by study participants with n=231 responses for asthmatics and n=64 for undiagnosed wheezers at age 18 yrs. ***: p<0.001; #: p=0.15; ¶: p=0.03.

TABLE 4 Environmental exposures for wheeze phenotypes

	Non-wheeze	Undiagnosed wheeze	Asthma
Smoke exposure			
Current personal smoking at age 18 yrs % (n/N)	26 (260/984)	47 (30/64)	34 (75/224)
p-value	Ref.	<0.001	0.10
Moderate-to-high urinary cotinine at age 18 yrs % (n/N)[#]	17 (78/467)	57 (16/28)	27 (33/123)[¶]
p-value	Ref.	<0.001	0.21
Any tobacco smoke exposure at age 18 yrs % (n/N)	41 (414/1008)	61 (39/64)	46 (106/232)
p-value	Ref.	0.006	0.67
Personal tobacco smoking (current or past) % (n/N)	45 (437/977)	73 (47/64)	54 (120/224)
p-value	Ref.	<0.001	0.051
Mean age started smoking yrs (n)	14.7 (408)	13.6 (41)	14.5 (113)
p-value	Ref.	<0.001	1.00
Mean number of cigarettes smoked per day	3.2 (254)	4.0 (29)	3.2 (73)
p-value	Ref.	0.001	1.00
Home tobacco smoke exposure during pregnancy (n/N)	45 (447/999)	58 (37/64)	46 (106/232)
p-value	Ref.	0.12	1.00
Paracetamol/NSAID use[+]			
Paracetamol use per month (n)	1.0 (0–2) (983)	1.0 (0–3) (63)	1.0 (0–3) (223)
p-value	Ref.	<0.001	<0.001
NSAID use per month (n)	0 (0–1) (983)	0 (0–1.5) (63)	0 (0–1) (223)
p-value	Ref.	<0.001	0.24
Males			
Paracetamol use per month (n)	0 (0–1) (534)	1.0 (0–2) (26)	1.0 (0–3) (101)
p-value	Ref.	0.09	<0.001
NSAID use per month (n)	0 (0–0) (508)	0 (0–1) (26)	0 (0–1) (101)
p-value	Ref.	0.009	0.51
Females			
Paracetamol use per month (n)	1.0 (0–2) (480)	2.0 (1–4) (37)	2.0 (0–3) (122)
p-value	Ref.	0.024	0.012
NSAID use per month (n)	0 (0–1) (480)	1.0 (0–3) (37)	0 (0–2) (122)
p-value	Ref.	0.06	0.42

Comparisons of wheeze phenotypes against non-wheeze reference (ref.) group. Chi-squared test was used for categorical data and ANOVA with Bonferroni correction for multiple comparisons with p-value determined at $p<0.05$. Mann–Whitney U-test applied for continuous data not showing normal distribution. NSAID: nonsteroidal anti-inflammatory drug. [#]: proportion of study participants having moderate-to-high urinary cotinine compared to total urinary cotinine tests in each wheeze group; [¶]: p-value for difference between undiagnosed wheeze and asthma, $p=0.002$; [+]: number of times taken per month; values are presented as medians with interquartile ranges and n participants that provided information in parentheses.

DISCUSSION

Wheezing illness in the form of either asthma or undiagnosed wheeze occurred in 22.8% of our study population at 18 yrs. Undiagnosed wheeze accounted for a fifth of these symptomatic subjects (4.9% of the whole population). As undiagnosed wheeze was defined as wheeze without asthma diagnosis, an initial assumption might be that this simply represented unrecognised asthma. Symptom frequency and severity in this group was similar to those with diagnosed asthma (whether treated or not). However, undiagnosed wheezers differed in several key characteristics from diagnosed asthmatics. At 18 yrs, they had significantly less atopy, no airflow obstruction or BDR and lower BHR than asthmatics, with values comparable to non-wheezers. Risk factor profiles for asthma and undiagnosed wheeze showed similar associations to asthmatic family history and personal rhinitis but differed in other important respects; personal smoking was a significant independent risk factor for undiagnosed wheeze but not asthma.

Our high cohort follow-up and abundant longitudinal data are key assets. However, the broader applicability of our findings might be questioned given the unique island environment and our study size. Nevertheless, our island population is genetically similar to mainland England (data on file) and our previous findings [25–27] have been similar to other international cohorts. Our present findings require replication in other birth cohorts and among larger samples. Reliance on questionnaire-based definitions of wheeze and asthma may be criticised, particularly where the label of asthma depends on a physician diagnosis. We used globally validated ISAAC questionnaires including a parameter encompassing therapy in our diagnostic criteria. The principal question ''have you ever had asthma'' was internally validated by asking specifically whether patients had formally received a physician diagnosis; that indicated outstanding agreement. A potential concern about our reference population of non-wheezers is whether they were tainted by a proportion of prior asthmatics. Separate multivariate models for undiagnosed

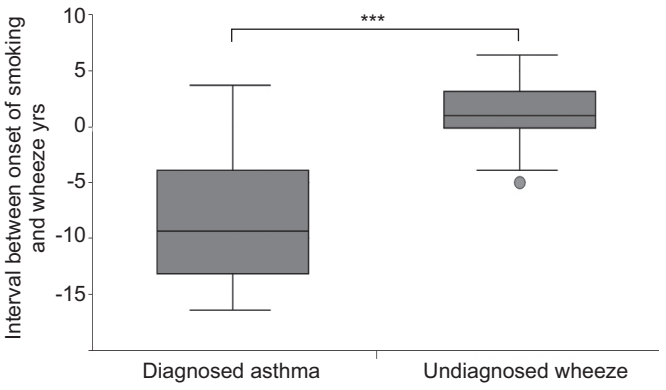

FIGURE 4. Wheeze onset in relation to smoking onset for asthma and undiagnosed wheeze at 18 yrs. Median duration and interquartile range from starting to smoke and first appearance of wheezing is shown for asthmatics and undiagnosed wheezers. Information on wheeze onset and smoking onset was collated from responses obtained at each study assessment. Analysis was by unpaired t-test. ***: $p<0.001$.

wheeze and asthma were explored after removing previous asthmatics from the non-wheeze group (online supplementary table E8); those did not alter our original principal findings suggesting that the influence of prior wheeze/asthma in the reference population at 18 yrs was minimal.

While asthma remains a clinical diagnosis, our asthma definition was validated by typical features of asthma; early life origins, strong associations to atopy throughout childhood, elevated *F*eNO at 18 yrs, airflow obstruction, significant BHR at both 10 and 18 yrs plus BDR at 18 yrs. Consistent with a growing body of evidence [14–16] these asthmatics also showed tracking of impaired childhood lung function into adulthood with impaired adolescent lung function gain. Diagnostic labelling of asthma in our population might appear better than anticipated from some studies [22–24]; however, that primary care practitioners can reliably distinguish wheezing representing asthma has been shown in a paediatric population by NYSTAD *et al.* [31]. In our population too, typical clinical features of asthma led to asthma diagnosis and therapy. Previous work has shown that without an asthmatic label, therapy of childhood wheezing is low [32]. Consistent with this none of the undiagnosed wheezers in our population received inhaled corticosteroids.

Undiagnosed wheeze in adolescence and early adulthood has gained minimal attention in the literature. Recent studies have demonstrated similar prevalence of undiagnosed asthma [22–24] to that of our undiagnosed wheeze group with comparable morbidity and undertreatment. Prior wheezing illness in undiagnosed wheeze was similar to non-wheezers, and was significantly lower than asthmatics, indicating a largely adolescent-onset condition. Given limited associations to atopy and normal *F*eNO, undiagnosed wheeze might represent a ''late-onset nonatopic asthma phenotype''. Yet undiagnosed wheezers showed no significant airflow obstruction or BHR at 10 or 18 yrs and low levels of BDR at 18 yrs, in sharp contrast to diagnosed asthmatics. Though asthmatics and undiagnosed wheezers differed in several characteristics, they both showed association to heritable and environmental influences. However, while asthmatic family history and paracetamol use were relevant to both, atopy was only significant in asthmatics, while smoking was only significant in undiagnosed wheezers.

TABLE 5 Multivariate analysis of factors associated with undiagnosed wheeze and asthma at 18 yrs

Risk factor	OR	95% CI	p-value
Undiagnosed wheeze			
Rhinitis at 18 yrs	2.82	1.38–5.73	0.004
Teenage smoking (past or current)[#]	2.54	1.19–5.41	0.02
Paracetamol use at 18 yrs[¶]	1.11	1.01–1.23	0.03
Family history of asthma[+]	2.26	1.10–4.63	0.03
Asthma			
Family history of asthma[+]	1.74	1.14–2.66	0.01
Atopy at 4 yrs[§]	3.98	2.52–6.28	<0.001
Rhinitis at 10 yrs	3.97	2.57–6.14	<0.001
Paracetamol use at 18 yrs[¶]	1.10	1.03–1.17	0.005

Factors for undiagnosed wheeze and asthma showing trends for significance at univariate analysis ($p<0.1$) were entered *en bloc* into separate logistic regression models to identify independent risk factors for each group. Factors entered for undiagnosed wheeze included female sex, family history of asthma, home tobacco exposure during pregnancy, atopy at 4 yrs, teenage smoking, paracetamol use at 18 yrs, nonsteroidal anti-inflammatory drug use at 18 yrs, and rhinitis at 18 yrs. Factors entered for asthma included female sex, family history of asthma, asthma/wheeze at 1 or 2 yrs, chest infections at 1 or 2 yrs, teenage smoking (past or current), atopy at 4 yrs, rhinitis at 10 yrs, paracetamol use at 18 yrs and number of days of exercise at 18 yrs. Factors showing multivariate significance ($p<0.05$) are shown. [#]: self smoking status current or past was determined at the 18 yr follow-up; [¶]: number of times (median values) paracetamol used per month; [+]: family history of asthma, determined at birth from parents; [§]: atopy defined by at least 1 skin test wheal response >3 mm diameter.

Audible wheeze in the absence of BDR or BHR could reflect irritant-induced bronchitis in response to substances like tobacco smoke. In most smoking undiagnosed wheezers, smoking onset preceded wheeze onset while the opposite was true in smoking asthmatics (fig. 4). These observations were supported by significantly higher urinary cotinine levels in undiagnosed wheezers. Our characterisation of undiagnosed wheeze may extend prior findings linking incident nonatopic wheeze and smoking. The British 1958 cohort showed smoking associations for what was termed incident asthma/wheezy bronchitis in early adulthood, more marked in nonatopics [33]. The definition of asthma/wheezy bronchitis in that study lacked validation by objective measures. It is conceivable that a considerable proportion of those labelled as asthma/wheezy bronchitis in that study may have had undiagnosed wheeze. COURT *et al.* [34] showed associations between nonatopic wheeze and smoking more marked in the absence of an asthma diagnosis that match our undiagnosed wheeze. Similarly, GENUNEIT *et al.* [35] found that personal smoking and incident wheeze/diagnosed asthma were associated in the 9–17 yr age period. They reported stronger smoking associations for wheeze over asthma and for nonatopics over atopics. In that study, incident wheeze was much commoner than incident asthma, suggesting considerable potential ''undiagnosed wheeze''.

In our study, only personal smoking retained significance for undiagnosed wheeze at multivariate analysis. Prior studies have shown persisting effects of maternal smoking in pregnancy/early life on childhood [12] and adult lung function [36]. It is impossible to disentangle tobacco exposures *in utero* from later passive and active exposures; synergism between differently timed exposures is likely to have existed in our study. Tobacco smoke exerts detrimental oxidative stress-related pulmonary effects. Conversely, the glutathione-S-transferase (GST) enzymes exert lung antioxidant activity. Associations exist between GST deficiency states, passive tobacco smoke exposure and asthma/wheeze risk [37] as well as impaired adolescent lung growth (worse in asthmatics) and genetic variants in that enzyme group [20]. Antioxidant defences may have some relevance to the undiagnosed wheezers defined in this paper. Paracetamol depletes glutathione levels, potentially facilitating airway damage and disease. Studies have suggested that paracetamol exposure at various stages of life increases asthma risk [11, 21, 38]. Assessment of paracetamol consumption has varied between studies. Most have used arbitrary cut-offs to define high paracetamol intake. BEASLEY *et al.* [39] recently chose a cut-off for paracetamol use of once or more per month as being significant in relation to asthma risk. While revealing statistically significant associations, the clinical significance of such cut-off values is unclear. For this reason and because paracetamol intake in our population was not normally distributed, we analysed median values for number of times taken per month in the past year. Our findings are limited by lack of precise data on dosage and indication. Confounding by indication or by reverse causality cannot be completely excluded, though previous studies do not support such concerns [21]. Our risk factor analysis for asthma at 18 yrs supported independent association between paracetamol use and asthma risk, consistent with prior literature. Similar associations with other wheezing disorders are poorly documented. MCKEEVER *et al.* [40] reported associations of paracetamol ingestion with both nonatopic asthma and COPD. This could be consistent with our findings associating paracetamol intake and personal smoking for undiagnosed wheezers. Female undiagnosed wheezers in our study had significantly elevated paracetamol consumption and significant impairment in adolescent lung growth that was additional to sex-mediated, and independent of height-mediated, effects. It is biologically plausible to speculate that paracetamol-impaired antioxidant defences might increase susceptibility to smoking-related oxidative airway damage and contribute to impaired adolescent lung function gain in female undiagnosed wheeze. Future mechanistic study of such possible interactions is warranted.

In conclusion, we found undiagnosed wheeze in 5% of young adults. Some characteristics of undiagnosed wheeze were similar to those of diagnosed asthma and some cases may represent ''undiagnosed asthma''. However, many typical asthma features were also absent in this group. Regarding all undiagnosed wheeze as simply ''undiagnosed asthma'' may be misplaced; they had significant disease morbidity and associations with potentially modifiable exposures including tobacco smoke and paracetamol. A key determinant of the relevance of adolescent undiagnosed wheeze will be reassessment of this group at future time points to determine its natural history plus potential relevance to adult respiratory disease such as asthma and COPD.

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STATEMENT OF INTEREST

None declared.

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