Indeed, the current classification moves to the right direction by adopting a clinically meaningful way of thinking and avoiding unnecessary pathophysiological implications; PH owing to left heart disease (Group 2) and chronic thromboembolism (Group 4) are good examples. In this context, sarcoidosis, PLCH and LAM (Group 5.2) represent disorders that, according to the current evidence, are associated with PH mainly due to lung involvement and, therefore, we propose their inclusion in the third category (PH owing to lung disease and/or hypoxia) in any future classification scheme.

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Predicting persistence of wheezing: one algorithm does not fit all

From the authors:

SCOTT *et al.* [1] have commented, in the light of outcomes of their ''Isle of Wight Birth Cohort study'' (IoWBC) [2, 3], on our findings on the risk factors for asthma in the Multicentre Allergy Study (MAS) birth cohort study [4]. We agree that the two studies lead to similar conclusions in regard to early origins of persistent wheezing, heterogeneity of childhood wheezing and the relevance of an atopic background. In addition, we followed their suggestion to build a prognostic score in accordance with the IoWBC [3] and to test its performance in the MAS database. Here we report the results of our analysis.

The IWBC prognostic algorithm comprises four risk factors: a family history of asthma; recurrent chest infections in infancy; absence of nasal symptoms at age 1 yr; and atopic sensitisation at age 4 yrs [3]. To make the data of the two cohorts comparable, we reduced our longitudinal study with follow-ups every year to the four time points of the Isle of Wight Study: age 1, 2, 4 and 10 yrs. Due to missing values, this reduction resulted in a fairly smaller population sample (n=765); therefore we increased the older age group by 8 and 9 yr olds and obtained a proportion of examined children similar to the one obtained in the IoWBC. The parameters we used were quite similar, although not identical, to those used in the IoWBC study (table 1). The frequency distribution of the risk score in the MAS cohort was similar to the one observed in the IoWBC; however, only three children with early wheezing had a risk score of 4 (table 2). A cut-off to predict persistent wheeze in the MAS cohort was therefore placed at a risk score of $\geqslant 3$. The positive predictive value (PPV) we obtained with this cut-off was 0.65 (95% CI 0.44–0.82) (table 3). Interestingly, when adopting a cut-off of 3, the PPV in the IoWBC study was 0.68, *i.e.* almost the same as the one obtained in the MAS cohort (table 3) [3].

On this basis we may conclude, as proposed by SCOTT *et al.* [1], that the IoWBC score can be a starting point in developing a clinically relevant predictive tool. Preventive measures should not be advised to children whose wheezing is likely to undergo spontaneous remission; therefore, a high PPV is desirable. On this basis, we feel that an algorithm based on early wheezing, sensitisation to mites and elevated allergen exposure, might be also clinically useful because it resulted in a better prediction in the MAS cohort (PPV 0.83). On the other hand, a third algorithm, based on the presence of atopic eczema, immunoglobulin (Ig)E sensitisation to food allergens and specific polymorphisms of the filaggrin gene, was able to predict another subset of asthmatic children of the MAS cohort with a PPV and equal to 1.00 (95% CI 65–100) [5]. Given the great heterogeneity of mechanisms and risk factors for wheezing disorders, multiple algorithms are likely necessary to predict, with enough confidence, persistence of wheezing in the children with early wheezing.

TABLE 1 Population examined, definitions and multivariate analysis for the persistence of early life wheezing

	IoWBC[#]	MAS
Children examined		
Enrolled n	1456	1314
Included in the analysis n (%)	1034 (71.0%)	936 (71.2%)
Wheezing		
Wheeze ever	Wheeze at any age: 1, 2, 4, or 10 yrs	Wheeze at any age: 1, 2, 4, 8, 9, 10 yrs
Incidence	417/1034 (40.3)	348/936 (37.2)
Early wheeze	Wheeze at age 1, 2, or 4 yrs	Wheeze at age 1, 2, or 4 yrs
Incidence	336/417 (80.6)	295/348 (84.8)
Late wheeze	Wheeze at age 10 yrs	Wheeze at age 8, and/or 9, and/or 10 yrs
Incidence	206/417 (49.4)	120/348 (34.5)
Transient wheeze	Early wheeze but no late wheeze	Early wheeze but no late wheeze
Incidence	211/336 (62.8)	228/295 (77.3)
Persistent wheeze	Early wheeze and late wheeze	Early wheeze and late wheeze
Incidence	125/336 (37.2)	67/295 (22.7)
Algorithm criteria and their association with persistence of early life wheezing		
Recurrent chest infections at age 2 yrs (OR; 95% CI)	>2 chest infections by age 2 yrs (1.99; 1.05–3.77)	>2 LRIs by age 2 yrs (1.01; 0.49–2.12)
Family history of asthma (OR; 95% CI)	Asthma in parents or siblings (2.31; 1.22–4.37)	Asthma in parents or siblings (1.68; 0.96–2.95)
Atopy (OR; 95% CI)	A wheal reaction of 3 mm or more to at least one of the allergens tested (list of allergens) at age 4 yrs (5.73; 2.95–11.12)	>0.7 KU·L^{-1} of IgE antibodies (CAP II or higher) against at least one of the allergen tested (list of allergens) at age <3 yrs (6.66; 3.5–12.7)
Nasal symptoms at 1 yr (OR; 95% CI)	Recurrent nasal symptoms/rhinitis (recurrent nasal discharge or blockage with attacks of sneezing and itchy eyes) (0.43; 0.19–0.96)	>2 episodes of runny nose in the first year of life (0.34; 0.19–0.59)

Data are presented as n/N (%), unless otherwise stated. IoWBC : Isle of Wight Birth Cohort study; MAS: Multicentre Allergy Study; Ig: immuglobulin. [#]: data as reported by KURUKULAARATCHY *et al.* [3].

A second point raised by SCOTT *et al.* [1] concerns the role of tobacco smoke and the genetic background in the determination of wheezing persisting up to puberty. The role of smoke and genetic predisposition in the MAS cohort has been recently published [6]. This study demonstrated that among children with two allergic parents, a mother who

TABLE 2 Prevalence and risk of wheezing outcome according to risk scoring system (table 1)

Risk score strata	IoWBC[#]				MAS			
	Wheezing outcome for each score		p-value	OR (95% CI)	Wheezing outcome for each score		p-value	OR (95% CI)
	Persistent	Transient			Persistent	Transient		
0	2/10 (20.0)	8/10 (80.0)	0.324	0.4 (0.08–1.83)	11/97 (11.3)	86/97 (88.7)	0.001	0.32 (0.16–0.65)
1	13/68 (19.1)	55/68 (80.9)	<0.001	0.3 (0.14–0.54)	26/122 (21.3)	96/122 (78.7)	0.630	0.87 (0.50–1.52)
2	32/101 (31.7)	69/101 (68.3)	0.058	0.6 (0.36–1.02)	15/53 (28.3)	38/53 (71.7)	0.283	1.44 (0.74–2.82)
3	42/64 (65.6)	22/64 (34.4)	<0.001	4.5 (2.46–8.19)	12/20 (60.0)	8/20 (40.0)	<0.001[¶]	6.00 (2.34–15.39)
4	10/12 (83.3)	2/12 (16.7)	0.002	8.7 (1.85–40.38)	3/3 (100.0)	0/3 (0.0)	0.011[¶]	

Data are presented as n/N (%), unless otherwise stated. IoWBC : Isle of Wight Birth Cohort study; MAS: Multicentre Allergy Study. [#]: data as reported by KURUKULAARATCHY *et al.* [3]; [¶]: comparisons are with Fischer's exact test where indicated by low cell counts.

TABLE 3 Performance for risk scoring system in the Isle of Wight Birth Cohort (IoWBC) and Multicentre Allergy Study (MAS) studies

Risk score strata	IoWBC[#]					MAS					
	Sensitivity	Specificity	PPV	NPV	LR+[¶]	Sensitivity	Specificity	PPV	95% CI for PPV	NPV	LR+[§]
>1	0.979	0.051	0.396	0.8	1.032	0.836	0.377	0.283	0.248–0.308	0.887	1.342
>2	0.845	0.404	0.475	0.808	1.418	0.448	0.798	0.395	0.303–0.487	0.831	2.219
>3	0.525	0.846	0.684	0.737	3.409	0.224	0.965	0.652	0.439–0.823	0.809	6.381
4	0.103	0.987	0.833	0.639	7.923	0.045	1.000	1.000		0.781	

PPV: positive predictive value; NPV: negative predictive value; LR+: positive likelihood ratio. [#]: data as reported by KURUKULAARATCHY *et al.* [3]; [¶]: LR+ refers to sensitivity/(1-specificity); [§]: the quality of a test/prediction is considered poor if LR+ is 1–3, acceptable if 3–10 and excellent if >10.

smoked regularly significantly increased the odds for allergic sensitisation (adjusted OR 4.8, 95% CI 1.3–18.2) and wheezing (adjusted OR 5.7, 95% CI 1.7–19.0) in her child compared with children who were never exposed. By contrast, maternal smoking had no effects in children without allergic parents. The results of the MAS cohort study therefore agree also in this respect with those obtained by IoWBC study and support the existence of gene-by-environment interaction (in our example ''atopic heredity-by-maternal smoke'' interaction) in the inception of asthma.

Similarities in the IoWBC and the MAS studies show that our research toward understanding the origins of asthma, by following the footsteps left by children developing persistent wheezing, is on the right track. We are probably starting to make good use of another Sherlock Holmes' famous aphorism: ''In solving a problem of this sort, the grand thing is to be able to reason backward'' [7].

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