Changing prevalence of wheeze, rhinitis and allergic sensitisation in late childhood: findings from 2 Isle of Wight birth cohorts' 12-years apart

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Short title: Time trends in wheeze, rhinitis and aero-allergen sensitisation

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ABSTRACT

Background: While the prevalence of asthma in children is decreasing or remaining the same, time-trends in the prevalence of rhinitis in children are not known. Understanding sensitisation trends may help inform about trends in asthma and rhinitis prevalence.

Objective: To assess time -trends of wheeze, rhinitis and aero-allergen sensitisation prevalence at 10 years of age we compared two birth cohorts established 12 years apart. To gain insight into differences in disease prevalence we assessed association of family-history, early life exposures and sensitisation with wheeze and rhinitis in each cohort.

Methods: The IoW (Isle-of-Wight) and FAIR (Food-Allergy-and-Intolerance-Research) unselected birth cohorts were established in 1989 and 2001 in IoW. Identical ISAAC questionnaire and Skin Prick test data were collected and compared at 10 years of age.

Results: Over the 12 year period from 2001 to 2012**,** prevalence of lifetime-wheeze, current-wheeze, and those ever-treated-for-asthma decreased by 15.9% (45.5-vs-29.6,$p<0.001$), 3.9% (18.9-vs-15, $p=0.020$) and 8.2% (31.7-vs-23.5, $p=0.001$) respectively. Conversely, current-rhinitis and lifetime-rhinitis prevalence increased by 5.5% (22.6-vs-28.1, $p=0.004$) and 13% (18.6-vs-31.7, $p<0.001$) respectively. Atopic status remained stable, however house dust mite (HDM) sensitisation decreased by 5.6% (19.2-vs-13.6, $p=0.004$) and grass sensitisation increased by 3.5% (12.9-vs-16.4, $p=0.054$). Male-sex, parental history of asthma and HDM sensitisation were significantly associated with lifetime-wheeze in both cohorts while maternal smoking during pregnancy was a significant risk factor only in the earlier IoW-cohort. Parental history of rhinitis and grass sensitisation were significantly associated with lifetime-rhinitis in both cohorts while HDM sensitisation was significant only for the IoW-cohort.

Conclusion: Contrasting changes were noted with falling wheeze and HDM sensitisation but rising rhinitis and grass sensitisation prevalence. Changing prevalence of aero-allergen sensitisations may explain the different time trends observed in these cohorts.

Key words: Time trends in UK, Asthma prevalence, allergic rhinitis, Hay fever prevalence, Sensitisation Prevalence

Abbreviations: IoW; Isle of Wight, FAIR; Food Allergy and Intolerance Research

INTRODUCTION

Asthma is the most common chronic disease affecting children [1] and rhinitis remains a significant health problem affecting quality of life[2]. There is global variation in asthma prevalence, with the point prevalence being higher in more affluent regions compared to less affluent regions [3, 4]. Globally asthma and rhinitis prevalence increased in the latter part of the 20th Century[5]. However global time trend studies in the last decade, showed that while childhood asthma prevalence continued to increase in less affluent regions with a low point prevalence, it was reaching a plateau in more affluent regions with higher point prevalence [6]. The United Kingdom (UK) has one of the highest asthma prevalence globally [4]. In UK, asthma and rhinitis prevalence increased from the 1970`s to mid-1990`s [5, 7]. However, time trends in asthma prevalence during the first decade of the 21st century are unclear, with some studies showing increase and others showing plateauing or decrease in asthma prevalence in schoolchildren [7-11].

It has been challenging to identify mechanisms driving changes in prevalence of allergic airway disease [12].Asthma is a complex disease where interaction of genetics and environment play an important role [13]. The temporal changes in asthma prevalence are too quick to be explained by naturally occurring genetic alterations in populations [6]. Allergic sensitisation to aero-allergens plays an important role; house dust mite (HDM) sensitisation is strongly associated with asthma [14-16]. Recent European studies of time trends in asthma prevalence have found that similar to asthma prevalence, aeroallergen sensitisation has remained stable from 1991 to 2001-02 in schoolchildren [17, 18]. Similarly allergic sensitisation is a strong risk factor for rhinitis [19] and it is known that grass pollen sensitisation is associated with rhinitis in the UK [20].

Meaningful analyses of time trends in changing prevalence of allergic disease require studies employing the same methodology and in the same geographical location over time.

Arshad et al have shown that HDM sensitisation is an important risk factor for asthma with an odds ratio of 8.07 (4.60–14.14) and sensitisation to grass was found to be an important risk factor for rhinitis with an odds ratio of 5.02 (2.21–11.41). We have previously reported the prevalence of current wheeze in the Isle of Wight (IoW) birth cohort at 10 years as 18.9% in 1999-2000 with associations to allergic sensitisation and sex [16]. We hypothesize that (i) the prevalence of wheeze and rhinitis will increase over a 12 year period and (ii) the increase in wheeze and rhinitis will be associated with a change in the same direction for house dust mite and grass pollen sensitisation respectively. Trends in prevalence of wheeze and rhinitis in UK have been reported till 2005; this paper looks at the continued trends till 2012 and also looks at time trends of aero-allergen sensitisations which have not been reported before in UK population. To investigate this, we compared current wheeze, lifetime wheeze, ever treated for asthma, current rhinitis symptoms, lifetime rhinitis and prevalence of allergic sensitisation to common aeroallergens at 10 years of age in two unselected population based birth cohorts established 12 years apart in the same county, the Isle of Wight, UK. Results in this paper are based on data of follow ups at 10 years of age of the IoW birth cohort [21] (1999-2000) and Food Allergy and Intolerance Research (FAIR) birth cohort [22] (2011-12).

METHODS

Study Population/Birth cohorts:

This is a repeat cross-sectional study performed in two separate cohorts of children aged 10 years, resident in the same locality and separated by 12 years. The Isle-of-Wight birth cohort (IoW-cohort) is a population based birth cohort established in 1989/90 for prospective study of asthma and allergic diseases. Children born between January 1989 and February 1990 on the Isle of Wight were recruited at birth (N=1536). Children have been reviewed at 1, 2, 4, 10 and 18 years[23]. The ten year follow up was done between 1999 and 2000. Food allergy and intolerance research (FAIR) is another population based birth cohort (N=969) established on

the Isle of Wight in 2001/02 for prospective study of allergic diseases [22]. Children were seen at 1, 2, 3 [24] and 10 year. The 10 year follow up was completed between 2011 and 2012. Table I gives a general description of both cohorts at their 10 year follow ups. Ethics approval was obtained at each follow-ups for both cohorts by local research ethics committees (FAIR: 10/H0504/11, IoW: No. 18/98), and informed consent was obtained from parents, and assent from participants.

Questionnaires:

ISAAC (International Study of Asthma and Allergies in childhood) and study specific questionnaires were used in both studies. Prevalence rates are based on parental responses to ISAAC questionnaires [25] used at 10 year follow ups in both cohorts. Lifetime wheeze symptoms were based on response to "Has your child ever had wheezing or whistling in the chest at any time in the past?" current wheeze was based on "Has your child had wheezing or whistling in the chest in the last 12 months?" and ever treated for asthma was based on "Has your child been treated for asthma?" Current rhinitis symptoms and lifetime rhinitis were derived from the responses to "In the past 12 months, has your child had a problem with sneezing, or a runny or blocked nose when he/she did not have a cold or the flu?" and "Has your child ever had hay fever?" respectively. Risk factors; family history of asthma or rhinitis, prenatal smoking and pet exposures were prospectively collected.

Sensitisation:

Allergic sensitisation was defined by positive Skin Prick Test (SPT) indicated by a wheal size of 3 mm or more than the negative control (Saline). Sensitisation to aero-allergens that were tested in both studies were compared; HDM (*Dermatophagoides pteronyssinus*), Cat (*Felis domesticus*) and Grass (mixed grasses) pollen. SPT was done using standardised allergen

reagents and methodology (ALK-Abell_o, Hørsholm, Denmark)[16, 22] and by the same research team.

Statistical Analysis:

The prevalence of wheeze, rhinitis and allergen sensitisation are given in proportions with 95% confidence intervals (95% CI). The significance of difference in prevalence between the two cohorts was tested using chi-square tests. Logistic regression analyses (Univariate and multivariate) were used to test the association of sex, family history, prenatal exposures and aero-allergen sensitisation with prevalence of wheeze and rhinitis. Backward stepwise model was used for multivariate regression analysis. All the analyses were done using SPSS Version 19 (IBM, Chicago, USA). CIA (Confidence Interval Analysis software) was used for 95% CI for proportions and the difference in prevalence. P value of less than 0.05 was considered significant.

RESULTS

Study population:

Of the 1456 children available for follow up in the IoW-cohort, 1373 (94%) provided questionnaire based information and 1036 (71%) underwent SPT at 10 years of age in 1999-2000. In the FAIR follow up at 10 years of age in 2011-12, 827 (85%) out of 969 available children responded to the questionnaire based information and 588 (61%) underwent SPT. Characteristics of the cohorts are displayed in Table I. The subsets who underwent SPT in both cohorts were representative of the respective cohorts (Supplementary Table E1).

Trend in Prevalence of wheeze, rhinitis and sensitisation

Prevalence of lifetime wheeze, current wheeze and ever treated asthma all decreased significantly from 1999-2000 to 2011-12. Conversely current rhinitis symptoms and lifetime rhinitis both increased significantly between these two time points (Table II).

Changes in prevalence for individual aero-allergen sensitisation varied according to allergen (Table III). HDM sensitisation decreased significantly, while grass pollen sensitisation increased (not significant) and cat sensitisation remained unchanged during the same period.

There was no difference in time trends of wheeze and rhinitis prevalence between IoW and FAIR cohorts when stratified by sex (Supplementary Table E2). The only difference noticed was in the increase in grass sensitisation from IoW to FAIR-cohort which was higher in girls compared to boys. Interactions of sex by cohorts were not significant for both lifetime wheeze and rhinitis (Supplementary Table E3).

Family history and prenatal risk factors

Overall, parental history of asthma was significantly higher in the FAIR-cohort compared to the IoW-cohort by 5.2% (p=0.012), which was significant for maternal (4.6%, p=0.009) but not paternal (2.5%, p=0.118) history. However sibling history of asthma significantly decreased by 5.1% (p=0.017). Parental history of rhinitis significantly increased from by 14.1% (p<0.001), which was significant for both maternal and paternal history of rhinitis. Sibling history of rhinitis showed non-significant increase of 1.7% (p=0.349). Maternal smoking during pregnancy showed a drop by 2.8% comparing the two time points but this was not significant and there was no difference in prenatal pet exposure in the two cohorts (Table IV).

Association of sex, family history and prenatal factors and aero-allergen sensitisation to wheeze and rhinitis

Lifetime prevalence of wheeze:

Male sex, parental history, sibling history, prenatal smoke exposure, HDM, grass and cat sensitisation were associated with wheeze in both cohorts in univariate analysis. Using backward stepwise multivariate logisitic regression male sex (p=0.038), parental history

(p<0.001), sibling history (p=0.008), maternal smoking during pregnancy (p=0.018) and HDM sensitisation (p<0.001) remained independently significant in the IoW-cohort while sex (p=0.007), parental history (p<0.001) and HDM sensitisation (p=0.004) remained independently significant in the FAIR-cohort (Table V). Therefore sex, parental history and HDM sensitisation were the common factors significantly associated with lifetime wheeze in both cohorts.

Lifetime prevalence of rhinitis:

Parental history and sensitisations to HDM, cat and grass were associated with lifetime rhinitis in both cohorts. Sibling history and prenatal maternal smoking in IoW and prenatal pet exposure in the FAIR-cohort were also associated with lifetime rhinitis using a univariate regression analysis. Using a multivariate regression with backward stepwise analysis, parental history (p<0.001), HDM (P<0.001) and grass (p<0.001) sensitisation remained significant in the IoW-cohort whereas only parental history of rhinitis (p<0.001) and grass sensitisation (p<0.001) remained significant in the FAIR-cohort (Table VI). Thus parental history of rhinitis and sensitisation to grass were common factors significantly associated with lifetime rhinitis in both cohorts.

Risk factors; HDM sensitisation and parental history of asthma for lifetime wheeze and grass sensitisation and parental history of rhinitis for lifetime rhinitis were tested for interaction with cohorts. Only cohort and parental history of asthma was significant (p=0.045) and all other interaction terms were not significant as summarised in supplementary table E4.

DISCUSSION

This study; comparing upper and lower airway disease symptom prevalence at 10 years of age in two population based birth cohorts 12 years apart in the same location has shown falling prevalence of current and lifetime wheeze plus ever being treated for asthma,

associated with HDM sensitisation which decreased during the same period. By contrast in the same period from 1999-2000 to 2011-12, there was an increase in current and lifetime rhinitis prevalence, which was associated with grass sensitisation which increased during the same period. Male sex, parental history of asthma and HDM sensitisation for wheeze and parental history of rhinitis and grass sensitisation remained significant risk factors in both cohorts for asthma and rhinitis respectively. Maternal smoking in pregnancy was significantly associated with lifetime wheeze only in the earlier IOW-cohort.

Time trend analysis can be challenging due to a number of factors including lack of uniformity in methodology and definitions of outcomes. We used identical validated questions (ISAAC) and the same methodology [25] which makes prevalence in our 2 cohorts comparable. Moreover, both cohorts in this study are population based, from the same geographical location and assessed by the same research team thus restricting the plausible biases and the influence of environmental differences when comparing the prevalence from wider geographical regions. Both cohorts have shown high follow up rates and the risk of significant bias is relatively low,. Other important aero-allergens like tree pollen and common moulds are missing in this study which can be one of the limitations of this paper, but the three aero-allergens studied usually explain majority of the atopic status[26]. Another potential limitation is the generalizability of the prevalence rates estimated on the IoW. Although, it remains a theoretical possibility, the population on the IoW is neither socially, not geographically, isolated. The prevalence rates for allergic diseases we have reported previously are very similar to the developed world in general and UK in particular [16]. Therefore, the time trends seen in our cohorts should be broadly generalizable. Also results from other islands have been comparable to the reference region on the mainland [27].

Anderson et al looked at ISAAC study results from UK centres from 1995 to 2002 in 12-14 year old UK children and reported an increase in ‘lifetime asthma’ (from 20.6% to 25.9%),

but decrease in current wheeze (from 33.9% to 27.5%)[9]. In the Aberdeen Schools Asthma Survey of 9-12 years old children, Malik et al assessed the time trends at three time points (1999, 2004 and 2009). Current wheeze (in the past 3 years) steadily decreased from 1999 to 2009 (27.9% in 1999, 25.2% in 2004, 22.2% in 2009), whilst 'lifetime asthma' prevalence showed temporal increase (from 24.3% to 28.4%) between 1999 to 2004 and then decreased from 2004 to 2009 (22.1%)[28]. Our results in similar age children (10 years old) confirm the continued decrease in prevalence of wheeze in the UK till 2012. The decrease in current and lifetime wheeze prevalence in our study is further substantiated by a concurrent fall in the prevalence of ever treated for asthma. In contrast to wheeze prevalence, we observed a significant rise in the prevalence of current rhinitis symptoms and lifetime rhinitis. Similar increasing trends for rhinitis have been reported in the UK looking at the primary care datasets from 2001 to 2005[29], however the Aberdeen schools asthma survey also showed a temporal increase in prevalence of ' lifetime rhinitis' from 1999 to 2004 (15.4% to 26.5%) but not much change between 2004 to 2009 (25.7%)[11].

As reported by Zollner et al in Germany and Braun-Fahrlander et al in Switzerland, we also found stable overall aero-allergen sensitisation on the Isle of Wight. However both studies reported mixed inhalant screen and differences in individual aero-allergen sensitisation were not investigated [17, 18]. We report a significant decrease in HDM sensitisation by 5.6% and a non-significant increase in grass sensitisation by 3.5%. In the Isle of Wight prevention study (different cohort from the 2 cohorts compared in this paper), reduction in the level of HDM mite was associated with reduced level of allergic sensitisation to HDM [30]. Based on this finding, it might be that falling HDM exposure levels may have contributed to the falling HDM sensitisation observed in our study. However, without HDM exposure information at two time points, this remains purely speculative but an important area for future research.

Allergic conditions are complex diseases where multiple environmental exposures, hereditary factors and gene-environment interactions play important roles [13]. One of the criticism for this paper would be not looking at all the plausible factors like decreasing birth rate, changes in family sizes, changes in living conditions and respiratory viral infections[12, 31]. Parental history is a known risk factor for developing allergic airway diseases [32, 33] and prenatal smoke exposure is associated with the development of asthma [33]. Prenatal smoke exposure declined which could be due to a better awareness of harmful effects of smoking particularly during pregnancy, and the association analysis suggested declining effect of prenatal smoke exposure on wheeze and rhinitis between these two cohorts. Parental history remained significantly associated to wheeze and rhinitis in both cohorts. We have shown that the prevalence of wheeze decreased in the current generation (in the cohort studied) and the sibling history of asthma also decreased, whereas the parental history of asthma increased between the two cohorts, suggesting different time trends in prevalence in two generations. Mothers of IoW-cohort, date of birth ranges from 1941 to 1973 (mean 1962) and for mothers of FAIR from 1956 to 1986 (mean 1973). It is plausible that the increase in the parent generation reflects increase in asthma prevalence observed in the latter half of 20th century.

HDM sensitisation is associated with lifetime wheeze and sensitisation to grass with lifetime rhinitis in both cohorts. Li et al. show that asthma prevalence continues to increase predominantly in HDM sensitised urban Chinese children[34]. An association does not necessarily imply causality; however one interpretation of our results is of a possible role of decreasing HDM and increasing grass sensitisations driving the contrasting time trends of wheeze and rhinitis prevalence respectively. Recently a synergistic effect of family history and second hand smoking has been shown for adult onset asthma [35]. There is a possibility of synergic effect of decreasing HDM sensitisation, decreasing prenatal smoke exposure and family history of asthma on decreasing wheeze prevalence and this provides an area for

further research. We did observe a decrease in the maternal smoking during pregnancy from IoW to FAIR-cohort but this change was not significant, so the interpretations have to be made with caution.

In conclusion, this is the first study reporting contrasting time trends for childhood allergic airway diseases along with aeroallergen sensitisations in the same geographical location; falling wheeze and rising rhinitis associated with falling time trends of HDM sensitisation with rise in grass pollen sensitisation. Changing associations with aero-allergen sensitisation and smoke exposure partly contribute to changing prevalence of wheeze and rhinitis.

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Table I: Descriptions of IoW and FAIR cohorts and 10 year follow up rates.

	IoW cohort	**FAIR cohort**
Birth year	1989-1990	2001-2002
Recruited at birth	1456	969
Male : Female	53% : 47%	51% : 49%
Period of 10 year FU	1999-2000	2011 - 2012
Questionnaire completed at 10 year	1373 (94%)	827 (85%)
SPT done at 10 year	1036 (71%)	588 (61%)

FU - Follow up, SPT- Skin Prick Test, IoW- Isle of Wight, FAIR-Food Allergy and Intolerance Research

Table II: Time trends in wheeze, asthma and rhinitis prevalence.

Characteristic	IoW 1999-2000 % (95% CI) n/N	FAIR 2011-12 % (95% CI) n/N	Difference % (95% CI)	p value
Lifetime Wheeze	45.5% (42.9 to 48.2) 625/1373	29.6% (26.6 to 32.8) 245/828	-15.9 (-19.9 to -11.8)	<0.001
Current Wheeze	18.9% (16.9 to 21.0) 259/1373	15% (12.7 to 17.6) 124/827	-3.9 (-7 to -0.6)	0.020
Ever treated for asthma	31.7% (29.2 to 34.3) 402/1267	23.5% (20.1 to 27.4) 120/510	-8.2 (-12.5 to -3.6)	0.001
Current rhinitis	22.6% (20.5 to 24.9) 308/1362	28.1% (25.1 to 31.2) 232/826	5.5 (1.7 to 9.3)	0.004
Lifetime rhinitis	18.6% (16.7 to 20.8) 256/1373	31.7% (26.9 to 36.8) 107/338	13.0 (7.8 to 18.5)	<0.001

n; proportion with feature, N; total number with responses to question

Table III: Time trends in prevalence of aero-allergen sensitisation

Aero-allergens	IoW 1999-2000 % (95% CI) n/N	FAIR 2011-2012 % (95% CI) n/N	Difference % (95% CI)	p value
HDM	19.2 (16.9 to 21.7) 199/1035	13.6 (11.1 to 16.6) 80/587	-5.6 (-9.2 to -1.8)	0.004
Cat	7.9 (6.4 to 9.7) 82/1035	7.7 (5.8-10.1) 45/586	-0.2 (-2.9 to 2.6)	0.861
Grass	12.9 (11.0 to 15.1) 134/1036	16.4 (13.6 to 19.6) 96/585	3.5 (-0.1 to7.2)	0.054
Any aeroallergen	25.7 (23.1 to 28.4) 266/1035	24.1 (20.8 to 27.7) 141/587	-1.6 (-5.9 to 2.8)	0.512

n; number of positive SPT to the allergen, N; total number tested for the allergen

Table IV: Prevalence of family history and prenatal exposures in both cohorts (irrespective of asthma or rhinitis in children)

Factor	IoW 1999-2000 % (95% CI) n/N	FAIR 2011-12 % (95% CI) n/N	Difference % (95% CI)	p value
Mother Hx of asthma	17.7 (15.7 to 19.8) 233/1317	22.3 (19.6 to 25.3) 184/825	+4.6 (1.2 to 8.2)	0.009
Father Hx of Asthma	13.9 (12.1 to 15.9) 183/1317	16.4 (14.0 to 19.1) 132/806	+2.5 (-0.6 to 5.7)	0.118
Parental Hx of Asthma	30.4 (28.0 to 33.0) 401/1317	35.7 (32.5 to 39.0) 289/810	+5.3 (1.1 to 9.4)	0.012
Sibling Hx of Asthma	31.4 (29.0 to 34.0) 414/1318	26.4 (23.3 to 29.7) 190/721	-5.0 (-9.1 to -0.9)	0.017
Mother Hx of Rhinitis	24.3 (22.0 to 26.7) 320/1318	33.9 (30.8 to 37.2) 280/825	+9.6 (5.7 to 13.6)	<0.001
Father Hx of Rhinitis	16.4 (14.5 to 18.5) 216/1316	25.1 (22.2 to 28.2) 202/804	+8.7 (5.2 to 12.4)	<0.001
Parental Hx of Rhinitis	37.1 (34.5 to 39.7) 489/1318	51.2 (47.7 to 54.6) 415/811	+14.1 (9.7 to 18.4)	<0.001
Sibling Hx of Rhinitis	19.3 (17.3 to 21.6) 255/1318	21.1 (18.3 to 24.2) 152/721	+1.8 (-1.9 to 5.5)	0.349
Mother smoked during pregnancy	25.2 (23.1 to 27.5) 384/1521	22.4 (19.9 to 25.2) 210/937	-2.8 (-6.2 to 0.7)	0.111
Any pet during pregnancy	50.4 (47.9 to 52.9) 765/1517	50.4 (47.2 to 53.5) 488/969	0 (-4.1 to 4.0)	0.974

Table V: Logistic regression analyses for association of Sex, aero-allergen sensitisations, heredity and prenatal exposures with lifetime wheeze

	IoW Cohort (1999-2000)					FAIR Cohort (2011-2012)				
	%	Univariate		Multivariate			Univariate		Multivariate	
	n/N	OR (95% CI)	p	OR (95% CI)	p	%	OR (95% CI)	p	OR (95% CI)	p
						Lifetime Wheeze				
Male sex	50.2 350/697	1.47 (1.19-1.82)	<0.001	1.32 (1.02-1.72)	0.038	32.9 140/425	1.39 (1.03-1.88)	0.030	1.81 (1.18-2.45)	0.007
HDM Sensitisation	67.8 135/199	2.76 (1.99-3.83)	<0.001	2.28 (1.58-3.31)	<0.001	56.3 45/80	3.84 (2.36-6.23)	<0.001	2.61 (1.36-5.03)	0.004
Grass Sensitisation	63.4 85/134	2.06 (1.42-3.00)	<0.001	-	NS	41.7 40/95	1.95 (1.24-3.06)	0.004	-	NS
Cat Sensitisation	68.3 56/82	2.50 (1.54-4.05)	<0.001	1.93 (1.08-3.44)	0.026	50.0 22/44	2.631 (1.42-4.89)	0.002	-	NS
Parental History	59.1 237/401	2.21 (1.74-2.81)	<0.001	2.00 (1.51-2.65)	<0.001	45.8 132/288	3.31 (2.42-4.54)	<0.001	2.82 (1.83-4.36)	<0.001
Sibling history	54.1 224/414	1.66 (1.32-2.10)	<0.001	1.47 (1.11-1.96)	0.008	41.1 78/190	2.08 (1.47-2.95)	<0.001	-	NS
Pet during pregnancy	45.5 317/697	1.01 (0.81-1.25)	0.944	-	NS	28.1 121/430	0.87 (0.64-1.17)	0.342	-	NS
Maternal smoking*	52.7 168/319	1.46 (1.14-1.88)	0.003	1.47 (1.11-1.96)	0.018	35.7 60/168	1.44 (1.00-2.06)	0.049	-	NS

Multivariate; backward stepwise model. % -proportion of the characteristic with wheeze (n/N), OR; Odds Ratio, 95% CI; 95% confidence interval, HDM; House dust mite. * Mother smoking during pregnancy.

Table VI : Logistic regression analysis for association of Sex, aero-allergen sensitisations, heredity and prenatal exposures with lifetime rhinitis

	IoW Cohort (1999-2000)					FAIR Cohort (2011-2012)				
		Univariate		Multivariate			Univariate		Multivariate	
	%	OR (95% CI)	p	OR (95% CI)	p	%	OR (95% CI)	p	OR (95% CI)	p
				Lifetime rhinitis						
Male Sex	18.8 131/697	1.020 (0.78-1.34)	0.885	-	NS	34.8 64/184	1.38 (0.87-2.19)	0.178	-	NS
HDM Sensitisation	44.2 88/199	4.55 (3.25-6.39)	<0.001	2.17 (1.42-3.32)	<0.001	60.6 40/66	4.83 (2.74-8.51)	<0.001	-	NS
Grass Sensitisation	64.9 87/134	11.51 (7.70-17.20)	<0.001	7.66 (4.79-12.26)	<0.001	77.6 66/85	18.79 (10.17-34.73)	<0.001	15.89 (7.711-32.76)	<0.001
Cat Sensitisation	56.1 46/82	6.06 (3.80-9.67)	<0.001	-	NS	75.7 28/37	8.93 (4.03-19.76)	<0.001	-	NS
Parental History	26.8 131/489	2.32 (1.75-3.07)	<0.001	1.91 (1.34-2.73)	<0.001	44.0 85/193	4.72 (2.72-8.20)	<0.001	4.21 (2.01-8.80)	<0.001
Sibling history	25.5 65/255	1.69 (1.22-2.34)	0.002	-	NS	45.9 28/61	1.26 (0.71-2.23)	0.428	-	NS
Pet during pregnancy	17.5 122/697	0.86 (0.66-1.13)	0.290	-	NS	26.2 45/172	0.59 (0.37-0.94)	0.028	-	NS
Maternal smoking*	14.1 45/319	1.52 (1.07-2.15)	0.020	**-**	**NS**	28.1 18/64	0.81 (0.45-1.49)	0.502	-	NS

Multivariate; backward stepwise model. % -proportion of the characteristic with rhinitis, OR; Odds Ratio, 95% CI; 95% confidence interval, HDM; House dust mite. * Mother smoking during pregnancy

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Supplementary information

Table (supplementary E1): Description of the subset with SPT and the whole cohorts.

	IoW 1999 - 2000			FAIR 2011 - 2012		
	Subset with SPT	Whole Cohort	p	Subset with SPT	Whole Cohort	p
Sex; Boys	49.8 (515/1035)	51.2 (786/1536)	0.494	52.3 (308/589)	51.0 (494/950)	0.916
Parental history of asthma	3 2.9 (323/981)	30.4 (401/1317)	0.220	36.0 (207/575)	35.7 (289/810)	0.910
Parental history of rhinitis	39.5 (388/982)	37.8 (489/1318)	0.242	55.0 (317/576)	51.2 (415/811)	0.156
Current wheeze	20.7 (214/1035)	18.9 (259/1373)	0.277	15.4 (91/589)	15.0 (124/829)	0.822
Current hayfever	25.9 (268/1035)	22.6 (308/1362)	0.067	31.9 (187/587)	28.1 (232/826)	0.140

Table (supplementary E2): Prevalence of wheeze, rhinitis and sensitisation by sex

	Boys			Girls		
	IoW 1999-2000	**FAIR 2011-12**	**p value**	**IoW 1999-2000**	**FAIR 2011-12**	**p value**
Lifetime wheeze	50.2 (350/697)	32.9 (140/425)	<0.001	40.7 275/676	26.1 (105/403)	<0.001
Current wheeze	21.5 (150/697)	17.2 (73/425)	0.077	16.1 (109/676)	12.7 (51/402)	0.125
Current rhinitis	22.7 (157/692)	28.1 (119/424)	0.043	22.5 (151/670)	28.1 (113/402)	0.040
Lifetime rhinitis	18.8 (131/697)	34.8 (64/184)	<0.001	18.5 (125/676)	27.9 (43/154)	0.009
HDM Sensitisation	22.5 116/515	16.9 52/307	0.055	16.0 83/520	10.0 28/280	0.020
Grass Sensitisation	16.3 84/516	18.4 56/305	0.443	9.6 50/520	14.3 40/280	0.046
Cat Sensitisation	8.0% 41/515	8.8% 27/306	0.665	7.9% 41/520	6.4% 18/280	0.452

Table E3: Sex by cohort interaction effects on lifetime wheeze and rhinitis.

Lifetime Wheeze		
	OR (95%CI)	**P**
Cohort	0.52 (0.40 – 0.67)	<0.001
Gender	1.47 (1.19 – 1.82)	<0.001
Cohort*Gender	0.95 (0.66 – 1.37)	0.776
Lifetime Rhinitis		
Cohort	1.71 (1.14 – 2.55)	0.009
Gender	1.02 (0.78 – 1.34)	0.885
Cohort*Gender	1.35 (0.79 -2.31)	0.275

Supplementary Table E4: Interactions of risk factors and cohorts for lifetime wheeze and rhinitis.

Lifetime wheeze		
HDM sensitisation	OR (95%CI)	P
Cohort (FAIR)	0.44 (0.34 – 0.56)	<0.001
HDM (Positive)	2.76 (1.99 – 3.83)	<0.001
Cohort*HDM	1.39 (0.77 – 2.50)	0.271
Parental asthma		
Cohort	0.39 (0.30 – 0.50)	<0.001
Parental Asthma	2.21 (1.74 – 2.81)	<0.001
Cohort* Parental Asthma	1.50 (1.01 -2.23)	0.045
Lifetime rhinitis		
Grass sensitisation	OR (95%CI)	p
Cohort (FAIR)	1.15 (0.78 – 1.70)	0.486
Grass (Positive)	11.51 (7.70 – 17.20)	<0.001
Cohort*Grass	1.63 (0.78 – 3.40)	0.190
Parental Rhinitis		
Cohort	1.77 (1.27 – 2.47)	0.001
Parental Rhinitis	1.69 (1.22 – 2.34)	0.002
Cohort* Parental Rhinitis	1.40 (0.72 – 2.73)	0.323