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Household chemicals, persistent wheezing and lung function: Effect modification by atopy?

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Abstract

Objectives: To assess the effects of mothers' domestic chemical use during pregnancy on wheezing and lung function in children up to 8.5 years and to explore the potential modifying effect of atopy.

Methods: In the Avon Longitudinal Study of Parents and Children (ALSPAC), a cohort study, a maternal composite household chemical exposure (CHCE) score was derived. Wheezing phenotypes from birth to 7 years were assigned on the basis of reported wheeze, lung function (FEV1, FVC, FEF_{25-75}) was measured at 8 ½ years and atopy by skin prick tests at 7 ½ years. Multinomial logistic and linear regression models assessed the relationship between wheezing outcomes, lung function and CHCE score, and interactions with atopy.

Results: Increased CHCE score was associated with early (<18m) and intermediate onset (18-30m) persistent and late onset (>30m) wheezing in non-atopic children (Adjusted Odds Ratio per z-score of CHCE [95% confidence interval] =1.41 [1.13, 1.76]; 1.43 [1.02, 2.13]; 1.69 [1.19, 2.41])). Increasing CHCE score was associated with decrements in FEV_1 and FEF_{25-75}.

Conclusion: Higher domestic chemical exposure during pregnancy was associated with persistent wheeze and lung function abnormalities in non-atopics. This may result from prenatal developmental effects or postnatal irritant effects on the developing airway, but is unlikely to be mediated through increased hygiene in the home.

Word count: 190

Introduction

In a previous study we reported that frequent use of household chemicals by pregnant women was associated with persistent wheezing in their offspring in early childhood.[1] There is a paucity of research into the possible effects of domestic chemical exposure in young children who spend a large proportion of their time indoors and who may be subject to a range of co-exposures in the home. However, despite several methodological differences, evidence from occupational studies can guide research into community and domestic exposures to indoor pollutants.[2] There is now substantial evidence of an increased risk of asthma in domestic and office cleaning workers that is likely to represent a direct causal effect of chemical exposure associated with these occupations[3], and other observational and case-control studies have reported positive associations between workplace exposure and a range of outcomes including asthma[4-5], occupational asthma[6-8], airway inflammation[9] and COPD.[10] A population-based case control study in Australia has recently reported higher levels of domestic exposure to VOCs in children with asthma compared with controls.[11]

One possible mechanism for this finding is that homes with more chemical exposure were cleaner and the risk of developing Th2 based diseases such as asthma was increased in association with reduced exposure to environmental antigens in early childhood.

The aims of this study were to investigate (i) the effects of maternal chemical use during pregnancy on wheezing patterns in children up to 7 years of age, (ii) whether increasing use is associated with decrements in lung function at 8½ years and (iii) whether atopy modifies these associations.

Methods

Study sample

The Avon Longitudinal Study of Parents and Children[12] is a prospective study of 14,541 pregnancies. Women were enrolled as early in pregnancy as possible, on the basis of an expected date of delivery between 1st April 1991 and 31st December 1992, and place of residence within the three Bristol-based health districts of the former county of Avon, UK. There were 14,062 live births, and 13,988 infants survived to one year. Ethical approval for the study was obtained from the ALSPAC Law and Ethics Committee and Local Research Ethics Committees.

Data collection

Wheezing

Questionnaires on wheezing patterns of the study child were completed by a parent or primary carer (usually the mother) at 6 months, 18 months, 30 months, 42 months and at 81 months after birth. Each mother was asked whether her child had experienced wheezing with whistling on his/her chest during the each of the study periods: 0-6 months; 6-18 months; 18-30 months; 30-42 months; 69-81 months. This information was used to identify six mutually exclusive patterns of wheeze between birth and 7 years: 1. never wheezed: no wheezing at any of the five time points; 2. early onset transient wheeze: wheezed 0-18 months but not 69-81 months; 3. intermediate onset transient wheeze: no wheeze 0-18 months & wheeze 18-42 months & no wheeze 69-81 months; 4. early onset persistent wheeze: wheeze 0-18 months & wheeze 69-81 months; 5. intermediate onset persistent wheeze: no wheeze 0-18 months & wheeze 18-42 months & wheeze 69-81 months; 6. late onset wheeze: onset of wheeze after 42 months and before 81 months.

Atopy

Skin prick tests were performed at the age of 7½ years to a panel of 6 allergens (house dust mite *(Dermatophagoides pteronyssinus)*, cat, mixed grass, mixed nuts, peanut and milk) and to positive (1% histamine solution) and negative (diluent) controls. Skin tests were carried out on the anterior surface of the left arm using new disposable sterile lancets for each allergen tested. The skin was pricked through a drop of allergen solution (ALK Abelló, Hoersholm, Denmark), the allergen solutions were blotted off after 5 minutes and the tests were read after a further 10 minutes. The maximum weal diameter was measured and a second measurement made at 90^{o} to the first. From these the mean weal diameter was calculated. For the purpose of this study, atopy was defined as any positive skin prick test to cat, mixed grass or house dust mite (weal diameter$\geq$1mm with a negative diluent response (0mm)).

Lung Function

Lung function was measured by spirometry at the age of 8½ years using a Vitalograph 2120 hand-held pneumotachograph and computer based analysis software (Spirotrac IV, Vitalograph, Maids Moreton, UK). Subjects were asked to postpone short acting bronchodilators for 6 hours, long acting bronchodilators, including oral bronchodilators and theophyilline for 24 hours and to avoid xanthine-containing beverages for 24 hours prior to testing. Testing was carried out in a dedicated research clinic by a team of 6 research physiologists. An on-screen incentive was used and interpretation of results was based on ATS/ERS criteria for acceptability and reproducibility of maximal expiratory flow volume curves (Miller et al 2005) and all flow volume curves were inspected post hoc to ensure that adequate criteria were met. Results were obtained from the best of three technically acceptable flow-volume curves repeatable within 200ml of forced vital capacity (FVC). The

variables FEV_1, FVC, FEF_{25-75} and FEF_{75} (maximal flow when 75% of VC had been expired) were recorded and transformed to standard deviation scores adjusted for age, sex and height (for full details see electronic data supplement).

Household chemical exposure

During pregnancy, women were asked to complete questionnaires on aspects of their health, environment and lifestyle. In particular, they were asked, "During this pregnancy how often have you used the following (a list of 15 chemical-based products)". Available responses were: not at all, less than once a week, about once a week, most days, every day. From the initial list of 15 products included in the questionnaire, the 11 most frequently used (at least 5% of study sample reported using the specific product) were selected. The products chosen (and the percentages of women using them) were: disinfectant (87.4%), bleach (84.8%), carpet cleaner (35.8%), window cleaner (60.5%), dry cleaning fluid (5.4%), aerosols (71.7%), turpentine/white spirit (22.6%), air fresheners (spray, stick or aerosol) (68%), paint stripper (5.5%), paint or varnish (32.9%) and pesticides/insect killers (21.2%). A simple score for frequency of use of each product was derived: 0 for not at all, 1 for less than once a week, 2 for about once a week, 3 for most days, 4 for every day. The scores for each product were summed to produce a composite household chemical exposure (CHCE) score for each respondent, which could range from 0 (no exposure) to 44 (exposed to all eleven products daily). These scores were then standardised (subtract mean and divide by standard deviation-z-scores) in order to make comparisons of effect sizes between analyses.

To investigate whether VOC-containing chemicals were more likely to be associated with the various outcomes, we also analysed the scores derived for VOC-containing chemicals and non-VOCs independently.

Potential confounding variables and effect modifiers

A number of variables were considered as potential confounders of the association between wheezing, lung function and CHCE score and are presented in Table 1 along with their associations with CHCE. Atopy as defined above was considered a possible effect modifier of the association between CHCE score and wheezing and lung function.

Statistical methods

All analyses were undertaken using SPSS for Windows (v 12.0). Multinomial logistic regression models were used to analyse associations between CHCE z-score and patterns of wheeze using the never wheezed group as the reference category. All models were adjusted for the above list of potential confounders that were associated with both outcome and exposure variables, but were not considered to be on the causal pathway. General linear models were used to analyse the effect of CHCE z-score on lung function SD scores (FVC, FEV_1, FEF_{25-75}) whilst controlling for confounders. CHCE z-score was considered as a continuous exposure variable in the first instance. However we also compared wheezing patterns and lung function of children whose mothers scored lowest in the CHCE score ($<10^{th}$ centile) to children whose mothers scored highest ($>90^{th}$ centile). For all outcome variables we tested whether atopy modified the observed associations with CHCE score using standard interaction tests within each of the models.

To assess whether a linear relationship with each wheezing pattern was appropriate, CHCE score was fitted as a continuous factor in a model and then as a categorical factor. For the categorical factor the CHCE score was split into deciles as there were only 28 discrete CHCE scores reported, ten groups providing adequate numbers per group. The likelihood ratio test

statistic was used to determine whether there was significant departure from linearity in the relationship between CHCE score and wheezing patterns.

Results

Of the 13988 ALSPAC children alive at one year, 7162 (51 %) children could be categorised into one of the six wheezing groups and had information available on chemical exposure in the home during pregnancy. Between birth and 7 years, 56.9% (N=4072) children never wheezed, 26.7% (N=1909) had early onset transient wheeze, 6.3% (452) had intermediate onset transient wheeze, 5.8 % (413) had early onset persistent wheeze, 2.1 % (149) had intermediate onset persistent wheeze and 2.3 % (167) had late onset wheeze.

In this sample, the CHCE score ranged between 0-30 with a mean of 9.4 (S.D. 4.1) and was approximately normally distributed.

Lung function measurements (with associated CHCE score) were available for 6359 children, of whom 100 reached FVC within 1 second and had no FEV_1 measurement calculated. All measurements are presented as standard deviation (SD) units.

In total, 6277 children underwent skin prick testing at 7.5 years and had an associated CHCE scores (21.6% atopic). CHCE score in atopic subjects (mean =9.4 (SD=4.0)) was similar to that in non-atopic subjects (mean = 9.5 (SD=4.1); (P=0.8)).

Table 1 presents characteristics of the study sample with respect to the confounding variables and their association with the CHCE score.

Children who wheezed, with the exception of those with early onset transient wheezing, were more likely to be atopic than children who never wheezed in this period. For example, in the never wheezed group 18% of children were atopic, compared with 16.5% in the early onset

transient group, 24.4% in the intermediate onset transient group, 48.6% in the early onset persistent group, 62.4% in the intermediate onset persistent group and 59% in the late onset wheeze group.

Wheezing patterns

Figure 1 presents the unadjusted and adjusted odds ratios (95% confidence intervals) for the defined wheezing patterns according to CHCE z-score as a continuous variable. Increasing CHCE z-score was strongly positively associated with early onset persistent wheeze and positively associated with the remaining wheezing phenotypes after adjustment for confounders. Adjustment by the confounders slightly attenuated the effect sizes of the univariable odds ratios and lengthened the 95% confidence intervals.

Atopic status at 7.5 years had a modifying effect on these associations (Figure 2), particularly for the non-transient wheezing groups. In non-atopic subjects the odds ratios (95% CI) per unit increase in z-score (equivalent to 4 points in CHCE or a non-user of a chemical versus a frequent user) for early onset persistent wheeze = 1.41 (1.13, 1.76); for intermediate onset persistent wheeze = 1.47 (1.02, 2.13); for late onset wheeze = 1.69 (1.19, 2.41) (P for interaction=0.001, 0.004, 0.006) (Figure 2a). The odds ratios for these groups in the atopic children were all less than one (Figure 2b).

The odds ratios [95% CI] for early onset persistent, intermediate onset persistent and late onset wheeze in non-atopic children who were most exposed (>90th centile of CHCE score) compared with the least exposed atopic children (<10th centile of CHCE score) were 4.10 [1.07, 15.76], 31.9 [1.48, 687.4] and 10.72 [1.54, 74.61], respectively. We did not further

adjust these figures due to the small numbers in the analyses (20% of initial sample used in this analysis).

Lung function

Lung volumes (FVC, FEV_1) and mid-expiratory flows (FEF_{25-75}) declined with increasing CHCE z-score (Table 3). However, the effect sizes were small (~ 1/5 SD per z-score increase in CHCE score). Although there is some suggestion of a differential effect of atopy on these associations, the effect sizes were small and the interaction tests not significant.

Figure 3 presents the odds ratios and 95% confidence intervals for the CHCE score using only VOCs and only non-VOCs. There is no appreciable difference in effect sizes between the two CHCE scores.

Discussion

Statement of principal findings

In a previous study we reported a positive association between frequent use of chemicals in the home and persistent wheezing in early childhood.[1] We have now confirmed that these associations persist for non-transient wheezing up to 7 years of age, and that they appear to be particularly strong in those children who are not atopic. This finding provides an argument against the role of the hygiene hypothesis as an explication of the association between chemical use and wheezing. In addition, we have observed that lung function variables at 8½ years are marginally lower in children whose mothers more frequently used chemicals in late pregnancy.

Methodological considerations

This was a large population based longitudinal study that collected exposure data during the study pregnancy and outcome data after delivery and was able to consider a large number of potential confounding variables within the statistical analyses.

It was not possible to determine whether the observed associations were due to *in utero* exposure or whether prenatal exposure was a proxy measure for general chemical use postnatally. We examined postnatal CHCE score (at 8 months post partum) and found a high correlation with the prenatal CHCE scores, and similar effect sizes for the outcomes, therefore it was not statistically possible to tease apart prenatal exposure from postnatal exposure. In addition, the CHCE is a crude score that weights all chemicals equally. Due to the nature of this study we were unable to investigate individual constituents, however we examined individual products and also dropped each product from the cumulative score one by one, but neither had an effect on any of the outcomes, confirming that no single product is implicated

in the observed associations. All analyses were then rerun using a CHCE score derived from VOCs only and one using non-VOCs. There did not seem to be a consistent pattern with either VOC or non-VOC containing chemicals in relation to wheezing phenotypes (Figure 3) or any of the other outcomes. It has to be accepted that reported use is only a broad indicator of mother/child exposure, but it is considered a reasonably robust measure as a previous validation study on a sub-sample of ALSPAC homes demonstrated a positive association between total VOC levels and self-reported use of air fresheners and aerosols.[12]

There was some selection bias amongst those who had complete data, that group having better educated, older mothers living in owner-occupied housing and fewer non-white children who weighed more at birth. In addition, those excluded from the analysis due to missing chemical exposure data were more likely to have wheezed at all ages than those included and those excluded from the analysis due to missing symptom data had, on average, higher chemical exposure scores than those in the analysis.

Interpretation of findings in relation to other studies

There is now substantial evidence of an increased risk of asthma in domestic and office cleaning workers that is likely to represent a direct causal effect of chemical exposure associated with these occupations. A recently published systematic review confirmed consistent associations between professional cleaning and asthma in six epidemiologic studies based on either population or case-control samples.[3] Compared with a reference population of administrative and clerical workers, Arif and colleagues reported an odds ratio of 2.37 for work-related asthma associated with cleaning in the NHANES III study.[7] Using similar comparison populations, Jaakkola et al [12] and LeMoual et al[4] also reported increased odds ratios associated with cleaning occupations but of smaller magnitude (1.42 and 1.04

respectively). Asthma has also been reported to be increased in current and former domestic cleaners compared with those never employed in domestic cleaning[5] while one study of domestic cleaners suggested that increased use of bleach among cleaners showed an exposure-response relationship for asthma when comparing intermediate with high exposure.[13] This has also been described in a case series of women exposed to domestic bleach-hydrochloric acid mixtures.[14] In this study, the prevalence of atopy was equivalent in cases and controls, suggesting that the increased risk for asthma was not mediated by allergic mechanisms, a finding that is consistent with a study of cleaners where non-atopics exposed to low MW agents had an increased risk of asthma compared with atopic workers.[15] Also, a surveillance study of work related asthma in the United States suggested that new cases were less likely to have an atopic basis than existing asthma that was work-aggravated.[16] While this association of repeated chemical exposure and asthma has been termed "low dose reactive airways dysfunction syndrome (RADS)" the term irritant induced asthma is more appropriate[17] as RADS is regarded as requiring a (usually single) high dose exposure to produce bronchial hyper-responsiveness. Our finding of increased risk for wheezing in non-atopic children exposed to high levels of household chemicals in early life, while it may be consistent with these observations, was based on exploration of the hygiene hypothesis rather than a prior hypothesis that atopy would interact negatively with chemical exposure and should therefore be subjected to confirmation in further studies. However, if true it gives rise to some potentially interesting insights into the mechanisms for the association between chemical exposure and wheezing illnesses in children.

It is plausible that the stronger effect observed in non-atopic subjects may be due to this particular exposure carrying a smaller risk compared to the potentially swamping effects of other exposures in atopic subjects.

These findings are consistent with the proposed possible contribution of occupational exposures to the development of or worsening of COPD[10] and the possibility thus exists that environmental exposures in early childhood might increase susceptibility to COPD in later life, particularly where they are associated with decrements in lung function, although the evidence for this is still largely conjectural. The question of whether lung function decrements associated with early life pulmonary insults are reversible remains to be resolved. Longitudinal lung function data from the Tucson study of children's respiratory health suggested that airway function abnormalities associated with asthma and wheezing illness that were established before 6 years of age did not change by age 16 years.[18]

In summary, our study has shown persistent effects on symptoms of wheeze and lung function in mid-childhood associated with exposures to a range of household chemicals during pregnancy particularly in non-atopic children. Further investigation is required to identify the specific agents responsible and the pathophysiologiocal mechanisms of this association.

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Table 1. Characteristics of study sample according to confounding variables and their association with CHCE score.

Table 2. Unadjusted and adjusted odds ratios (95% confidence intervals) for wheezing phenotypes according to CHCE z-score, and stratified for atopy.

Table 3. Unadjusted and adjusted regression coefficients for CHCE z-score and lung function measures in all children and stratified for atopic status.

Figure 1. Unadjusted and adjusted odds ratios for wheezing phenotypes according to CHCE z-score.

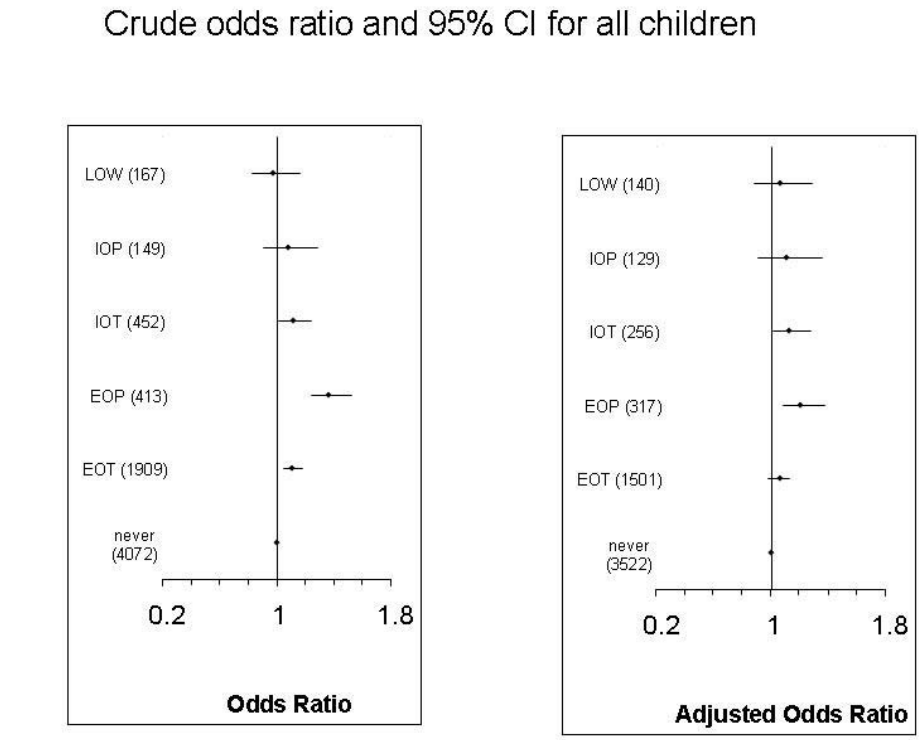


Fig 1

Figure 2. Adjusted odds ratios (95% confidence intervals) for wheezing phenotypes according to CHCE z-score-stratified by atopy at 7.5 years.

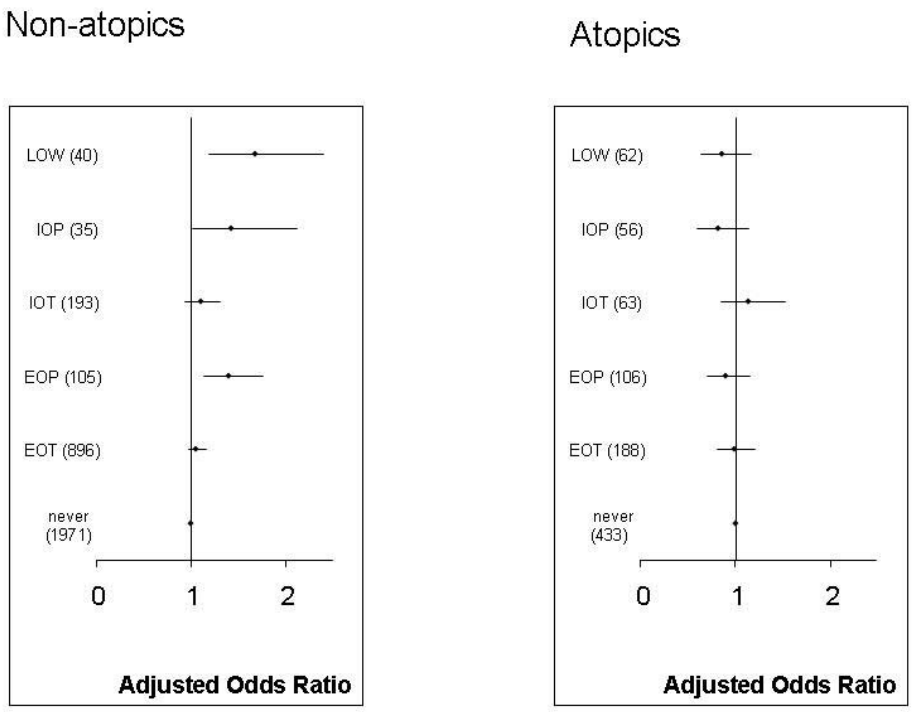
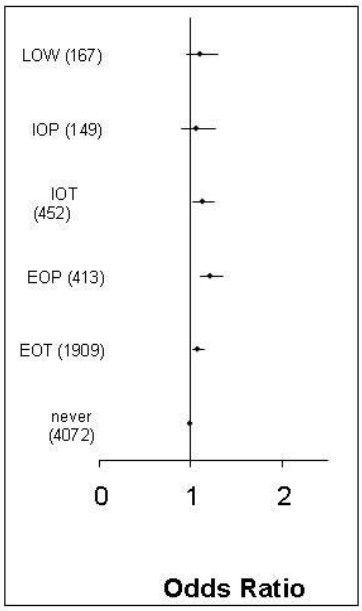


Fig 2

Figure 3. Adjusted odds ratios (95% confidence intervals) for wheezing phenotypes according to a) CHCE z-score for VOCs and b) CHCE z-score for non-VOCs

Score for VOCs



Score for non-VOCs

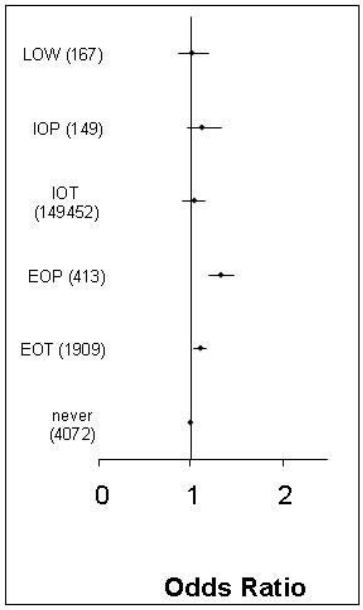


Fig 3

Never: never wheezed
LOW: Late Onset Wheeze
IOP: Intermediate Onset Persistent
IOT: Intermediate Onset Transient
EOP: Early Onset Persistent
EOT: Early Onset Transient

Table 1. Characteristics of study sample according to confounding variables and CHCE score.

	Boys	Girls	CHCE
	%(n)	%(n)	Mean (SD)
Maternal smoking during pregnancy			
None	85.2 (3057)	85.4 (2858)	9.1 (4)
1-9 per day	6.5 (234)	6.0 (202)	10.3 (4)
10+ per day	8.3 (296)	8.5 (286)	11.1 (4)
ETS			
No	69.7 (2563)	67.6 (2323)	9.0 (4)
Yes	30.3 (1116)	32.4 (1111)	10.2 (4)
Damp housing			
No	49.9 (1782)	52.2 (1752)	9.6 (4)
Yes	50.1 (1787)	47.8 (1607)	9.1 (4)
Pets in home			
No	46.7 (1670)	46.2 (1555)	9.1 (4)
Yes	53.3 (1907)	53.8 (1810)	9.8 (4)
Maternal history of asthma			
No	88.8 (3257)	89.0 (3033)	9.4 (4)
Yes	11.2 (410)	11.0 (375)	9.5 (4)
Maternal age at delivery			
<25 years	14.0 (521)	15.6 (539)	10.4 (4)
>=25 years	86.0 (3190)	84.4 (2912)	9.2 (4)
Maternal highest education			
None/CSE	13.3 (487)	13.6 (464)	10.7 (4)
Vocational	8.6 (315)	8.3 (281)	10.6 (4)
O level	36.3 (1325)	35.1 (1194)	9.9 (4)
A level	25.7 (938)	26.5 (902)	8.9 (4)
Degree	16.1 (590)	16.45 (563)	7.1 (4)
Housing tenure			
Mortgaged owned	84.6 (3025)	82.8 (2788)	9.2 (4)
Council rented	8.6 (306)	9.0 (303)	11.3 (5)
Other	6.9 (245)	8.3 (278)	8.8 (4)
Crowding in home			
<= 0.5 person per room	15.8 (555)	15.4 (509)	8.7 (4)
0.5 – 0.75 person per room	38.7 (1356)	39.4 (1299)	9.2 (4)
0.75 – 1 person per room	34.2 (1199)	34.6 (1142)	9.7 (4)
> 1 person per room	11.2 (394)	10.5 (347)	10.1 (4)

Maternal parity							
0		45.3 (1651)		46.4 (1569)		9.1 (4)	
1		35.4 (1290)		36.3 (1227)		9.6 (4)	
2+		19.4 (707)		17.3 (585)		9.8 (4)	
Hours mum works outside home							
Don't work		51.2 (1780)		51.1 (1657)		9.5 (4)	
<10 hours		7.9 (276)		8.6 (278)		9.3 (4)	
10-20 hours		21.5 (748)		22.6 (732)		9.5 (4)	
20-30 hours		9.5 (329)		8.2 (266)		9.1 (4)	
30+ hours		9.9 (345)		9.5 (309)		8.7 (4)	
Season of questionnaire							
Jan-April		39.7 (1461)		40.3 (1377)		9.2 (4)	
May-August		33.3 (1226)		33.3 (1137)		9.8 (4)	
September-December		26.9 (991)		26.4 (902)		9.3 (4)	

Table 2. Odds ratios (95% confidence intervals) for wheezing phenotypes according to CHCE z-score.

		Unadjusted -all	**Adjusted – all***		**Adjusted – non-atopic**	**N**	**Adjusted - atopic**	**N**	**P****
	N	7162	5987			3240		908	
Wheezing phenotype									
Never wheezed		1.00 (ref)	1.00 (ref)		1.00 (ref)	1971	1.00 (ref)	433	-
Early onset transient		1.11 [1.05-1.18]	1.07 [0.99-1.14]		1.06 [0.97-1.16]	896	0.99 [0.81-1.22]	188	0.8
Early onset persistent		1.37 [1.24-1.53]	1.21 [1.08-1.38]		1.41 [1.13-1.76]	105	0.89 [0.69-1.15]	106	0.001
Intermediate onset transient		1.12 [1.01-1.24]	1.13 [1.01-1.28]		1.11 [0.94-1.31]	193	1.13 [0.84-1.52]	63	0.7
Intermediate onset persistent		1.08 [0.91-1.29]	1.11 [0.91-1.36]		1.47 [1.02-2.13]	35	0.82 [0.59-1.13]	56	0.004
Late onset		0.98 [0.83-1.16]	1.07 [0.88-1.29]		1.69 [1.19-2.41]	40	0.85 [0.63-1.16]	62	0.006

** P for interaction.

* Adjusted for overcrowding in home, highest maternal education level, housing tenure, gender, exposure to environmental tobacco smoke, maternal history of asthma, maternal parity, maternal age at delivery, smoking during pregnancy, month of completion of chemicals questionnaire, hours mum worked outside home.

Table 3. Regression coefficients (Standard errors) for CHCE z-score for lung function measures in all children and stratified for atopic status.

		Unadjusted -all	**Adjusted - all**		**Adjusted – non-atopic**		**Adjusted - atopic**		**P for interaction**
FVC		-0.031 (0.013)	-0.026 (0.016)		-0.03 (0.02)		-0.012 (0.04)		0.3
FEV1		-0.044 (0.013)	-0.044 (0.016)		-0.052 (0.02)		-0.005 (0.04)		0.2
FEF $_{25-75}$		-0.032 (0.013)	-0.033 (0.016)		-0.046 (0.02)		0.021 (0.041)		0.4