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The relationship between infant lung function and the risk of wheeze in the preschool years

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Abstract

Rationale—Premorbid infant lung function predicts childhood wheeze, but it is unclear whether lower infant lung function is most closely associated with atopic or non-atopic preschool wheeze.

Objective—To examine the association between premorbid infant lung function and preschool wheeze according to atopic or non-atopic wheeze phenotype. Additionally, to explore the relations of ADAM33 polymorphism with lung function during infancy, preschool wheeze and atopy.

Methods—Infant lung function was measured in147 healthy term infants aged 5-14 weeks. Raised volume rapid thoracoabdominal compression was performed to determine $FEV_{0.4}$. Atopic status was determined by skin prick testing at 3 years and wheeze ascertained from parental questionnaires (1 and 3 years). ADAM33 polymorphisms were examined using haplotype analysis.

Measurements and Main Results—Early infancy $V'max_{FRC}$ and $FEV_{0.4}$ were lower in those who wheezed in the first year (p=0.002 and p=0.03), and lower $V'max_{FRC}$ was associated with wheeze in the third year (p=0.006). Non-atopic children who wheezed in their third year of life had lower $FEV_{0.4}$, compared to non-atopic children who did not wheeze (p=0.02), whilst atopic children with wheeze did not (p=0.4). No ADAM33 haplotype was associated with infant lung function, preschool wheeze or atopy after correction for multiple testing.

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Conclusions—Lower premorbid infant lung function was present in infants who subsequently wheezed during the first and third years of life. Lower $FEV_{0.4}$ was associated with non-atopic wheeze but not atopic wheeze at 3 years of age. The relation between ADAM33 polymorphism, infant lung function and preschool wheeze requires examination in larger studies.

Keywords

wheeze; asthma; infant lung function; preschool; ADAM Proteins

Introduction

Lower infant lung function is a risk factor for wheeze in infancy and early childhood[1-4]. Previous studies have demonstrated abnormalities of infant lung function are present in those children who subsequently experience wheeze and these abnormalities can be detected prior to the first wheezing illness[1-4].

Lower levels of respiratory function soon after birth have been shown to precede and predict the development of wheezing illnesses during the first year of life[5] and also the first three years[6]. The results of longer-term follow up studies are less consistent. Although tracking of lung function from infancy, through childhood[7] and into adult life[8] is well described, the relationship between early lung function and phenotypes of wheezing illness is less clear. The Tucson study studied 125 infants and found that reduced $V'max_{FRC}$ in the first 6 months of life was associated with transient wheeze but not with wheezing after 3 years of age[9]. In contrast, other studies suggest early impairment of lung function is a risk factor for wheeze which persists into later childhood[7;10].

The original 'wheeze phenotypes' derived from the the Tuscon study were defined retrospectively based on age of onset and persistence of symptoms[9]. In a cohort prospectively phenotyped using clinical features[11] thought to be associated with later asthma, high risk infants have been found to have lower forced expiratory volumes at 8-20 months than wheezy infants at lower risk of subsequent asthma[12]. However, this study of high risk infants did not measure premorbid infant lung function nor establish the relationship between lung function and clinical wheeze phenotype in an unselected population. It is not clear how premorbid infant lung function relates to the atopic and non-atopic wheeze phenotypes.

Common genetic polymorphism is known to impact neonatal disease and outcome[13] and reduced early life lung function may be, in part, genetically determined. ADAM33 is a positionally cloned asthma susceptibility gene that shows strongest linkage with a combined asthma and bronchial hyperresponsiveness phenotype[14]. ADAM33 is expressed in lung fibroblasts and bronchial smooth muscle and is expressed during embryonic lung development[15]. Previously, ADAM33 polymorphisms have been associated with impaired lung function at 3 years of age, specifically deficits in FEV_1 and carriers homozygous for the A allele of F+1 SNP had double the risk of transient early wheeze[16].

The Southampton Women's Survey was the first to measure premorbid $FEV_{0.4}$ in a longitudinal pregnancy cohort study[17]. Using this outcome measure, we aimed to explore the associations between premorbid infant lung function and preschool wheeze according to atopic phenotype. As a secondary aim, we explored the relationship between ADAM33 polymorphism, lung function in infancy and preschool wheeze.

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Methods

Participants

The Southampton and South West Hampshire Local Research Ethics Committee approved the protocol and written consent was obtained from the children's mothers. Detailed information regarding the participants and infant lung function testing have been described[17]. In brief, caucasian infants, born at at least 37 weeks gestation without major congenital anomalies and prior to any respiratory infection were recruited from the Southampton Women's Survey (SWS), a population-based birth cohort[18]. Lung function was measured, between May 1999 and October 2002, when the infants were 5-14 weeks old.

Lung function was measured, with infants lying supine, in quiet sleep augmented with chloral hydrate. An inflatable jacket connected to a rapid inflation system was placed around the infant's chest and abdomen and a leak-free facemask with Fleisch pneumotachograph (Dynasciences, Blue Bell, CA) was held over the nose and mouth. Data were collected using RASP software (Physiologic Ltd, Newbury, Berks, UK) and analysed in SQUEEZE (Paul Dixon, London).

Respiratory rate was measured during tidal breathing. As previously described[17], partial expiratory flow-volume loops were obtained by performing a rapid thoracoabdominal compression (RTC) at end tidal inspiration and $V'max_{FRC}$ calculated. Compliance of the respiratory system (Crs) was calculated from flow-volume curves performed at raised volumes (RV) performed by passive inflation at 30cm water. At least two acceptable, reproducible (within 10%)[17] raised volume and partial expiratory curves were obtained. $FEV_{0.4}$ and FVC were obtained from flow-volume curves recorded at raised volume RTC. For each infant, $FEV_{0.4}$ and Crs were calculated from the best raised volume loop ($FEV_{0.4}$ plus FVC) and the best $V'max_{FRC}$ was used. For each outcome there were approximately 100 infants with acceptable lung function data as recording each measure of lung function was not possible for all infants.

Symptoms

Mothers completed contemporaneous respiratory symptom diaries during their child's first year of life, and at ages one and three years they completed a questionnaire which included the question 'has your child experienced any episodes of chestiness associated with wheezing or whistling in his/her chest since they were last seen?'. Skin reactivity to cat[a], dog[a], house dust mite[a] (Dermatophagoides pteronyssinus), milk[a], grass pollens[a], and egg[b] was assessed at age 3 years (Hollister-Stier, Spokane, WA[a], Alyostal, Antony, France[b]). Atopy was defined as a wheal to any allergen at least 3mm in diameter in the presence of appropriate control results.

Genotyping

DNA was isolated from cord blood using a salting-out procedure[19]. The following five SNPs were chosen for genotyping as they span the ADAM33 gene region (based on the LDU map from Simpson *et al*[16]). ADAM33 SNPs Bp1 (rs487377), Fp1 (rs511898), STp7 (rs574174), Vm3 (rs628977), V4 (rs2787094) were genotyped by TaqMan SNP genotyping assays (Table E1).

Statistical Analysis

The infant lung function data were logarithmically transformed to achieve normality and adjusted for age and sex where necessary. t-tests were used to assess differences between geometric mean group values of infant lung function measurements according to wheeze status at 1 and 3 years, and after subdividing the 3-year wheeze group according to atopic

status. Agreement between the parent-completed symptom diaries and the nurse-administered questionnaires was assessed by weighted Kappa (κ) analysis.

ADAM33 haplotype quantitative trait and power analysis were performed using Haploscore (Haplo.stats R package version 1.3.8.)[20] in R (version 2.5.1)[21] with the additive haplotype effect model.

Assuming 50 children in each outcome group, there is 80% power at the 5% level of significance to detect a difference of 0.57 SDs in any infant lung function measurement between the two outcome groups. Matched genotype and lung function data were available for 103 children for respiratory rate, 82 for Crs, 105 for V'max$_{FRC}$ and for 76 children for FEV$_{0.4}$.

Results

147 infants had lung function measurements, of which 146 provided questionnaire data at age one year, 141 provided questionnaire data at 3 years of age and 113 had skin prick testing. Symptom diaries were returned by 102 mothers. There was strong concordance between the symptom diaries and questionnaires for the reported incidence of wheeze, (κ =0.71, p<0.001). Given this, all subsequent analyses are based upon questionnaire data. A total of 114 DNA samples were available for ADAM33 SNP genotyping; genotype assignment approached 99% (6 failed PCR reactions out of a total 570) with a maximum of two unassigned genotypes for each SNP and all genotype frequencies were in Hardy-Weinberg Equilibrium. (See online supplement).

During the first year of life, 74 infants had at least one episode of wheezing. Thirty three children experienced wheeze in the third year of life, of these 23 had also experienced wheeze in the first year of life whilst 10 had not. Of the 113 children who were skin prick tested for allergy, 20 (17.7%) had at least one positive reaction and were classed as atopic. Of the children who experienced wheeze 75% were atopic and 25% were not.

The demographic characteristics of those children reporting wheeze at 3 years and those that did not are listed in table 1. Comparing children who did and did not wheeze, there were no differences in gender or the mother's age, atopy but those who wheezed at 3 years were more likely to have a mother who smoked during pregnancy. However, those who wheezed in the first year of life were more likely to be born to younger mothers and have mothers who had smoked in pregnancy than those who did not wheeze.

Associations between wheeze or wheeze phenotype and lung function were examined after adjusting for factors that were found to influence measures of lung function on univariate analysis. FEV$_{0.4}$, and V'max$_{FRC}$ were adjusted for gender and Crs for gender and age at testing.

Relationship between infant lung function and respiratory symptoms reported at age 1 year

V'max$_{FRC}$, FEV$_{0.4}$ and Crs were lower in infants who subsequently wheezed in their first year than in those who did not by 22.5% (p=0.002), 8.1% (p=0.03) and 6.8% (p=0.04) respectively (Table 2). The group mean respiratory rate was 6.8% higher in the wheeze group than in the non-wheeze group (p=0.03).

Relationship between infant lung function and respiratory symptoms reported at age 3 years

V'max$_{FRC}$ was 23.2% lower in infants who wheezed in their third year than in those who did not (Table 3) (p=0.006). However, there were only small non-significant differences in $FEV_{0.4}$, Crs and respiratory rate between the two groups. When non-atopic children were considered separately from atopic individuals, $FEV_{0.4}$ was 11% lower in those who wheezed (p=0.02) (Table 4). There were no significant differences in any measure of infant lung function when atopic children with wheeze in the third year were compared to atopic children without wheeze (Table 5).

ADAM33 SNP haplotype analysis—No ADAM33 SNP haplotype was significantly associated with infant lung function measurements after adjusting for multiple testing by Bonferroni correction (Table 6). However, one rare ADAM33 haplotype (GACTG; Hap Freq = 0.014) indicated a possible association with increased Crs measurements (Tables 6 and E4; corrected P value = 0.062). Haplopower analysis (Online Data Supplement) revealed that with the small sample size (n = 82) we were underpowered (Power = 19%) to detect a common haplotype (freq = 18%) association accounting for 5% of the variance in the mean of the Crs measurement.

Discussion

This study demonstrates an association between impaired premorbid infant lung function and preschool wheezing illness. This confirms the results of previous studies[4;6]. Our analyses show for the first time that lower lung function in early infancy is a risk factor for non-atopic wheeze, rather than atopic wheeze. Additionally, this study is the first to report reduced $FEV_{0.4,}$ prior to lower respiratory infection, as a risk factor for wheeze in the preschool years.

Premorbid measures of forced expiratory volume in 0.4 seconds ($FEV_{0.4}$) during infancy as a predictor of wheeze have not previously been studied, though reduced $FEV_{0.5}$ following symptoms has been reported in wheezy children aged 8 – 20 months12. Lung function measures derived from raised volume expiratory manoeuvres are believed to discriminate better between healthy individuals and those with respiratory disease when compared to tidal breathing measures[22;23]. $FEV_{0.4}$ provides a more robust measure of infant lung function than V'max$_{FRC}$[24]. Furthermore, $FEV_{0.4}$ is well suited to longitudinal study as it is intuitively more comparable to the measures of lung function, such as FEV_1, which are used in older children and adults.

The results of this study may be of relevance to the general population. We recruited healthy infants and only excluded those born before 37 weeks gestation to prevent bias due to effects of prematurity upon lung development. Our results demonstrate that variations in measures of expiratory flow measured in unselected populations are associated with preschool wheeze.

Small study numbers limited the exploration of lung function measures according to wheeze phenotype. However, a significant difference in $FEV_{0.4}$ was noted in non-atopic children who wheezed during the third year of life compared to non-atopic children without wheeze. There was no difference in any measure of infant lung function when atopic children with wheeze in the third year were compared to non-atopic children without wheeze. This may have been partly related to greater power associated with a more balanced distribution of non-atopic than atopic individuals between the wheeze and no wheeze groups. However, others have speculated that wheezing during the first year of life is often a transient

condition due to reduced airway caliber and that wheeze beginning or persisting into later childhood is more likely to be due to the wheeze phenotype recognized as asthma[4].

Due to the small numbers involved it was not possible to analyse our data according to age of onset. However, the broader confidence intervals and divergence of results between atopic and non-atopic individuals at age three years may be evidence of comparative heterogeneity of wheeze phenotypes later in childhood. The strong association between reduced measures of forced expiratory flow and wheeze at one year may reflect a common underlying mechanism, similar to that proposed by Martinez, whereby initial airway diameter, length or other characteristics might predispose certain infants to wheezing with viral respiratory infections[3]. With growth this may resolve in some infants as airway size increases but for those with the smallest airway dimensions the risk of non-atopic wheeze may persist. In contrast, airway dimensions at birth may be less significant in the aetiology of atopic wheeze compared to other factors acquired in association with an atopic phenotype.

As described earlier, ADAM33 is expressed in the embryonic lung[15] and SNPs in the gene encoding ADAM33 were previously found to predict impaired lung function at age 3 and 5 years[16]. However, it is unclear whether ADAM33 polymorphism is associated with abnormal lung function at birth (reflecting altered *in utero* lung development) or whether post-natal gene-environment interaction alters lung function and increases risk of asthma. Recent observations from the PIAMA birth cohort show that *in utero*, but not post natal, cigarette smoke exposure interacts with ADAM33 polymorphism to determine childhood lung function and BHR would suggest that ADAM33 polymorphism may alter *in utero* lung development[25]. In the current study, no ADAM33 haplotype was associated at the 5% level with lung function or symptoms in the first or third years of life after correction for multiple testing, however one rare haplotype was significantly associated with Crs uncorrected P value = 0.0048). Simpson *et al.* described that the F+1 polymorphism explained 3% of the variance in lung function (sRaw) at 3 years of age[16]; power calculations show that we only had 19% power to detect an association that predicts 5% variance in Crs measurements. Given the observation of interaction with *in utero* smoke exposure and the trend towards association seen in the current study, the association between ADAM33 haplotypes and infant lung function needs to be examined in a meta-analysis of data from all available infant lung function cohorts.

In summary this study has shown a significant relationship between early life lung function including $FEV_{0.4}$ and respiratory symptoms in the first and third years of life. This is further evidence suggesting that pre-natal factors contribute to the development of wheeze in early life.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Dezateux C, Stocks J, Dundas I, Fletcher ME. Impaired airway function and wheezing in infancy: the influence of maternal smoking and a genetic predisposition to asthma. American Journal of Respiratory & Critical Care Medicine. 1999; 159:403–410. [PubMed: 9927350]
2. Murray C, Pipis SD, McArdle EC, Lowe LA, Custovic A, Woodcock A, National Asthma Campaign-Manchester Asthma and Allergy Study Group. Lung function at one month of age as a risk factor for infant respiratory symptoms in a high risk population. Thorax. 2002; 57(5):388–92. [PubMed: 11978912]
3. Martinez FD, Morgan WJ, Wright AL, Holberg CJ, Taussig LM. Diminished lung function as a predisposing factor for wheezing respiratory illness in infants. New England Journal of Medicine. 1988; 319(17):1112–7. [PubMed: 3173442]
4. Young S, Arnott J, O'Keeffe PT, Le Souef PN, Landau LI. The association between early life lung function and wheezing during the first 2 yrs of life. European Respiratory Journal. 2000; 15:151–157. [PubMed: 10678638]
5. Murray AB, Ferguson AC, Morrison B. Airway responsiveness to histamine as a test for overall severity of asthma in children. Journal of Allergy & Clinical Immunology. 1981; 68(2):119–24. [PubMed: 7251999]
6. Martinez FD, Morgan WJ, Wright AL, Holberg C, Taussig LM. Initial airway function is a risk factor for recurrent wheezing respiratory illnesses during the first three years of life. Group Health Medical Associates. American Review of Respiratory Disease. 1991; 143:312–316. [PubMed: 1990945]
7. Turner SW, Palmer LJ, Rye PJ, Gibson NA, Judge PK, Cox M, Young S, Goldblatt J, Landau LI, Le Souef PN. The relationship between infant airway function, childhood airway responsiveness, and asthma. American Journal of Respiratory & Critical Care Medicine. 2004; 169(8):921–7. [PubMed: 14764431]
8. Sears MR, Greene JM, Willan AR, Wiecek EM, Taylor DR, Flannery EM, Cowan JO, Herbison GP, Silva PA, Poulton R. A longitudinal, population-based, cohort study of childhood asthma followed to adulthood. New England Journal of Medicine. 2003; 349(15):1414–22. [PubMed: 14534334]
9. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. New England Journal of Medicine. 1995; 332(3):133–8. [PubMed: 7800004]
10. Haland G, Carlsen KC, Sandvik L, Devulapalli CS, Munthe-Kaas MC, Pettersen M, Carlsen KH, ORAACLE. Reduced lung function at birth and the risk of asthma at 10 years of age. New England Journal of Medicine. 2006; 355(16):1682–9. [PubMed: 17050892]
11. Castro-Rodriguez JA, Holberg CJ, Wright AL, Martinez FD. A clinical index to define risk of asthma in young children with recurrent wheezing. American Journal of Respiratory & Critical Care Medicine. 2000; 162(4 Pt 1):1403–6. [PubMed: 11029352]
12. Borrego LM, Stocks J, Leiria-Pinto P, Peralta I, Romeira AM, Neuparth N, Rosado-Pinto JE, Hoo AF. Lung function and clinical risk factors for asthma in infants and young children with recurrent wheeze. Thorax. 2009; 64(3):203–9. [PubMed: 19008296]
13. Harding D. Impact of common genetic variation on neonatal disease and outcome. Archives of Disease in Childhood Fetal & Neonatal Edition. 2007; 92(5):F408–13. [PubMed: 17712190]
14. Van EP, Little RD, Dupuis J, Del Mastro RG, Falls K, Simon J, Torrey D, Pandit S, McKenny J, Braunschweiger K, Walsh A, Liu Z, Hayward B, Folz C, Manning SP, Bawa A, Saracino L, Thackston M, Benchekroun Y, Capparell N, Wang M, Adair R, Feng Y, Dubois J, FitzGerald MG, Huang H, Gibson R, Allen KM, Pedan A, Danzig MR, Umland SP, Egan RW, Cuss FM, Rorke S, Clough JB, Holloway JW, Holgate ST, Keith TP. Association of the ADAM33 gene with asthma and bronchial hyperresponsiveness. Nature. 2002; 418:426–430. [PubMed: 12110844]
15. Haitchi HM, Powell RM, Shaw TJ, Howarth PH, Wilson SJ, Wilson DI, Holgate ST, Davies DE. ADAM33 expression in asthmatic airways and human embryonic lungs. American Journal of Respiratory & Critical Care Medicine. 2005; 171(9):958–65. [PubMed: 15709049]

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16. Simpson A, Maniatis N, Jury F, Cakebread JA, Lowe LA, Holgate ST, Woodcock A, Ollier WE, Collins A, Custovic A, Holloway JW, John SL. Polymorphisms in a disintegrin and metalloprotease 33 (ADAM33) predict impaired early-life lung function. American Journal of Respiratory & Critical Care Medicine. 2005; 172:55–60. [PubMed: 15805180]
17. Lucas JS, Inskip HM, Godfrey KM, Foreman CT, Warner JO, Gregson RK, Clough JB. Small size at birth and greater postnatal weight gain: relationships to diminished infant lung function. American Journal of Respiratory & Critical Care Medicine. 2004; 170(5):534–40. [PubMed: 15172897]
18. Inskip HM, Godfrey KM, Robinson SM, Law CM, Barker DJ, Cooper C, SWS Study Group. Cohort profile: The Southampton Women's Survey. International Journal of Epidemiology. 2006; 35:42–48. [PubMed: 16195252]
19. Miller SA, Dykes DD, Polesky HF. A simple salting out procedure for extracting DNA from human nucleated cells. Nucleic Acids Research. 1988; 16(3):1215. [PubMed: 3344216]
20. Sinnwell, JP.; Schaid, DJ.; Yu, Z. haplostats: Statistical Analysis of Haplotypes with Traits and Covariates when Linkage Phase is Ambiguous. Available from http://mayoresearch.mayo.edu/mayo/research/schaid_lab/software.cfm
21. R Development Core Team. R: A language and environment for statistical computing R Foundation for Statistical Computing. Vienna: 2008.
22. Ranganathan SC, Bush A, Dezateux C, Carr SB, Hoo AF, Lum S, Madge S, Price J, Stroobant J, Wade A, Wallis C, Wyatt H, Stocks J. Relative ability of full and partial forced expiratory maneuvers to identify diminished airway function in infants with cystic fibrosis. American Journal of Respiratory & Critical Care Medicine. 2002; 166(10):1350–7. [PubMed: 12421744]
23. Turner DJ, Lanteri CJ, Lesouef PN, Sly PD. Improved detection of abnormal respiratory function using forced expiration from raised lung volume in infants with cystic fibrosis. European Respiratory Journal. 1994; 7(11):1995–9. [PubMed: 7875271]
24. Ranganathan SC, Hoo AF, Lum SY, Goetz I, Castle RA, Stocks J. Exploring the relationship between forced maximal flow at functional residual capacity and parameters of forced expiration from raised lung volume in healthy infants. Pediatric Pulmonology. 2002; 33:419–428. [PubMed: 12001274]
25. Reijmerink NE, Kerkhof M, Koppelman GH, Gerritsen J, de Jongste JC, Smit HA, Brunekreef B, Postma DS. Smoke exposure interacts with ADAM33 polymorphisms in the development of lung function and hyperresponsiveness. Allergy. Jun; 2009 64(6):898–904. [PubMed: 19236319]

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At a Glance Commentary

Scientific Knowledge on the Subject

Reduced infant lung function is a risk factor for childhood wheeze, but it is not known whether lower premorbid lung function is most closely associated with atopic or non-atopic wheeze. Polymorphisms in ADAM33 have been shown to predict lung function at 3 years of age, but the relationship between such polymorphisms and infant lung function has not previously been explored.

What This Study Adds to the Field

This study demonstrates that children who wheeze at 1 or 3 years have lower premorbid infant lung function than children who do not wheeze, particularly if they are non-atopic. Within this study, ADAM33 polymorphisms were not related to lower lung function in first few years of life.

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Table 1

Characteristics of those children reported to wheeze at 3 years of age compared to those who were not

	Children reported to wheeze at 3 years (n=33)	Children not reported to wheeze at 3 years (n=108)	P-value
Maternal age at child's birth (years), mean (SD)	29.7 (4.2)	30.3 (3.3)	0.3
Maternal smoking during pregnancy, (%)	27.3	12.3	0.04
Male gender, (%)	54.6	49.1	0.6
Maternal atopy, (%)	48.3	43.3	0.6

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Table 2

Infant lung function measures by whether the infant wheezed in the first year of life or not

	No wheeze			Wheeze			Percentage increase/decrease	
	n	Mean	95%CI	n	Mean	95%CI	%	95%CI
$V'max_{FRC}$ *	70	149.0	133.3 to 166.5	72	115.4	103.3 to 129.0	−22.5%	−33.7% to −9.5%
$FEV_{0.4}$ *	49	143.3	136.4 to 150.7	49	131.8	124.0 to 140.1	−8.1%	−15.0% to −0.6%
Crs **	52	49.4	47.3 to 51.6	56	46.0	43.7 to 48.5	−6.8%	−12.8% to −0.3%
Respiratory rate	69	42.8	41.1 to 44.5	72	45.7	43.8 to 47.7	6.8%	0.8% to 13.1%

*Adjusted for age

**Adjusted for age and sex

Results are geometric mean values. Percentage increase is calculated from the logged values of the respiratory measures

Table 3

Infant lung function measures by whether the infant wheezed in the third year of life or not

	No wheeze			Wheeze			Percentage increase/decrease	
	n	**Mean**	**95%CI**	**n**	**Mean**	**95%CI**	**%**	**95%CI**
$V'max_{FRC}$ *	106	139.2	126.5 to 153.1	32	106.8	93.0 to 122.7	−23.2%	−36.4 % to −7.3%
$FEV_{0.4}$ *	73	139.6	133.8 to 145.7	25	128.6	118.4 to 139.6	−7.9%	−15.5% to 0.3%
Crs **	79	48.0	46.2 to 49.8	29	46.8	43.1 to 50.7	−2.5%	−9.8% to 5.4%
Respiratory rate	106	44.1	42.6 to 45.7	31	45.2	42.9 to 47.7	2.5%	−4.6% to 10.1%

*Adjusted for age

**Adjusted for age and sex

Percentage increase is calculated from the logged values of the respiratory measures

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Table 4

Infant lung function measures by whether the infant wheezed and was not atopic in the third year of life or neither wheezed nor was atopic

	No wheeze and no atopy			Wheeze and no atopy			Reduction/increase in those who wheezed and were not atopic	
	n	Mean	95%CI	n	Mean	95%CI	%	95%CI
$V'max_{FRC}$ *	71	135.0	119.8 to 152.1	20	107.1	87.5 to 131.1	−20.6%	−37.9% to 1.5%
$FEV_{0.4}$ *	49	139.0	132.2 to 146.2	16	123.7	114.6 to 133.5	−11.0%	−19.2% to −2.0%
Crs **	56	48.6	46.4 to 51.0	19	45.8	41.3 to 50.9	−5.8%	−14.7% to 4.1%
Respiratory rate	71	45.5	43.4 to 47.6	20	43.8	40.6 to 47.2	−3.7%	−12.3% to 5.7%

* Adjusted for age

** Adjusted for age and sex

Percentage increase is calculated from the logged values of the respiratory measures

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Table 5

Infant lung function measures by whether the infant wheezed and was atopic in the third year of life or neither

	No wheeze and no atopy			Wheeze and atopy			Reduction/increase in those who wheezed and were atopic	
	n	Mean	95%CI	n	Mean	95%CI	%	95%CI
$V'max_{FRC}$ *	71	135.0	119.8 to 152.1	7	108.5	87.1 to 135.2	−19.6%	−45.3% to 18.1%
$FEV_{0.4}$ *	49	139.0	132.2 to 146.2	5	148.9	110.1 to 201.3	7.1%	−9.6% to 26.9%
Crs **	56	48.6	46.4 to 51.0	6	51.8	45.5 to 59.0	6.5%	−8.2% to 23.6%
Respiratory rate	71	45.5	43.4 to 47.6	6	49.1	45.0 to 53.5	7.9%	−7.8% to 26.3%

* Adjusted for age

** Adjusted for age and sex

Percentage increase is calculated from the logged values of the respiratory measures

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Table 6
Summary of results of haplotype analysis of ADAM33 with uncorrected P values < 0.1.

Phenotype	adam33bp1	adam33fp1	adam33stp7	adam33vm3	adam33v4	Hap-Freq[a]	Hap-Score[b]	Uncorrected P-value[c]	Corrected P-value[d]
Respiratory rate (n= 103)	G	G	C	T	G	0.02351	-2.13291	0.0329	0.43
Crs (n = 82)	G	A	C	T	C	0.0137	2.8227	0.0048	0.06
V'maxFRC (n= 105)	A	G	C	T	G	0.07069	-1.85387	0.0638	
	A	A	T	T	C	0.03186	1.65231	0.0985	
Atopy (n= 82)	G	A	T	C	G	0.04798	2.40585	0.0161	0.24
Atopic wheeze (n= 57)	A	G	C	T	G	0.0539	1.89707	0.0578	

[a] Only haplotypes with a greater then 1% frequency presented.

[b] Positive z-score means the haplotype associates with increased measurement (continuous variable) or presence of a trait (binomial).

[c] P values <0.1 are highlighted in bold.

[d] Significant P-values (< 0.05) were adjusted for multiple testing by Bonferroni correction (p-value multiplied by number of ADAM33 haplotypes with frequency > 0.005). Full analyses are presented in the on-line data supplement (Tables E4-E12).