Thorax Online First, published on April 11, 2008 as 10.1136/thx.2008.096388

Lifecourse predictors of adult respiratory function: results from the Newcastle Thousand Families Study.

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Running Title: Respiratory function at age 49-51

Keywords: cohort, epidemiology, fetal programming, FEV_1, lower respiratory tract infections

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Word count (excluding title page, references, figures and tables) = 3832

Reference count = 34

ABSTRACT

Background:

Impaired development *in utero* is suggested to increase the risk of poor respiratory health in adulthood, although a consensus has not been reached. A possible explanation for discrepancies between previous studies is inconsistent controlling for potential confounding factors, particularly childhood infections. Also, little is known regarding the relative importance of factors operating at different stages of the lifecourse. We have used detailed longitudinal data from the Newcastle Thousand Families cohort to assess the impact of birth weight, and various other factors acting throughout the lifecourse, on predicting forced expiratory volume in one second (FEV_1).

Methods:

Detailed information was collected prospectively during childhood, including birth weight, childhood infections, and socio-economic circumstances. At age 49-51, 412 study members attended for clinical examination and measurement of FEV_1. These data were analysed in relation to a range of factors from across the lifecourse using linear regression models.

Results:

After adjustment for all other significant variables, increasing birth weight - standardised for sex and gestational age - ($p=0.011$), being breast fed for more than four weeks ($p=0.017$), less frequent childhood lower respiratory tract infections (LRTI) ($p=0.015$), non smoking ($p<0.001$), lower body fat percentage ($p=0.010$), male sex ($p<0.001$), no history of asthma ($p=0.013$), and greater adult height ($p<0.001$) were all independently associated with higher adult FEV_1.

Conclusion:

Adult lung function is influenced by numerous factors during an individual's lifetime, acting both directly and indirectly throughout the lifecourse. As expected, sex, height, and smoking were the most important predictors of FEV1, but birth weight, breast feeding, and childhood LRTIs also contributed significantly.

INTRODUCTION

The fetal programming hypothesis proposes that impaired development *in utero* increases the risk of adverse health in adulthood.[1] A number of previous epidemiological studies have examined this hypothesis in the context of respiratory health. Although most identified that lower birth weight was associated with lower adult forced expiratory volume in the first second (FEV_1), some found no evidence of such a relationship.[2]

One potential reason for these conflicting results is the difficulty of determining the additional influence of lower respiratory tract infections (LRTIs) in early childhood, the risk of which may itself be partly determined by size at birth and gestational age, in addition to other factors such as social class in early childhood. This presents a particular problem in studies where details of early infections have not been collected prospectively during childhood. Childhood LRTIs have been previously shown to predict reduced lung function in later life.[3-8]. These infections may lie on the causal pathway between fetal growth and adult respiratory health. In addition, factors such as gestational age and sex have not always been taken into account.[9] Gestational age is especially important for lung function since preterm infants have the added complication of immature lungs.

The effects of other factors on respiratory health, such as infant feeding and social class in childhood, as well as smoking, social class and occupational exposures to dust and fumes in adulthood, also need to be taken into account, in order to assess the relative magnitude of factors operating at different stages of life. The Newcastle Thousand Families cohort, consisting of all 1142 infants born in May and June 1947 to mothers residing within the city of Newcastle upon Tyne (northern England) provides a unique opportunity to apply a lifecourse approach to adult respiratory function. Two-thirds of these children were followed until the age of 15 years, with detailed information collected prospectively on their health, growth, and socioeconomic circumstances,[10] and all available individuals were reassessed at age 49 - 51. We used data collected prospectively at birth, during childhood and at age 49-51 to identify significant predictors of FEV_1 with the aim to establish the relative importance of risk factors acting throughout the lifecourse.

METHODS

Participants in the current investigation were members of the cohort who either were traced through the National Health Service Central Register or contacted the study team in response to media publicity in the mid 1990's. Data on fetal and infant life and childhood had been collected prospectively. Between October 1996 and December 1998, questionnaires on health and lifestyle were completed and study members attended for clinical examination.[10-12] Ethical approval for the study was obtained from the appropriate Local Research Ethics Committees and all participants gave their written informed consent.

Clinical assessment

FEV_1 was measured using a portable spirometer (Vitalograph Compact II, Vitalograph, Buckingham, UK) by one of two trained research nurses. The highest value from a minimum of three attempts was recorded for each individual. An interobserver error of 1.4% and an intraobserver error of 2.2% were observed. Exhaled carbon monoxide was measured using a carbon monoxide monitor (Smokerlyzer; Bedfont Scientific; Rochester, Kent, UK). Height and weight were recorded and percent body fat was estimated from bioelectrical impedance measured using a Holtain body composition analyser (Holtain Ltd, Crymych, Wales, UK).

Measurement of early life experience

Information on a number of factors, including birth weight, gestational age, infant feeding, social class, and housing conditions were recorded prospectively for all study members. Birth weights, as recorded by the midwife, were standardised for gestational age and sex.[13] Social class was defined according to the UK Registrar General's Standard Occupation Classification [I (assumed to be the most advantaged), II, III non-manual, III manual, IV, and V (assumed to be the least advantaged)] using paternal occupation at birth. Housing conditions were assessed by the city's Public Health Department, and scored for the presence of overcrowding, lack of hot water, toilets shared between households, and dampness or poor repair. Over the following fifteen years, episodes of illness were reported to the study team by health visitors, who visited the families regularly throughout childhood, and general practitioners if a child presented to them with an illness. The study team was also informed whenever the children were referred to, or attended, hospital. To minimise attrition, only illness records from the first five years are used in this study. Measles, whooping cough, tuberculosis, and influenza were coded as dichotomous variables ('ever had', 'never had'), while the number of episodes of LRTIs (defined as episodes of bronchitis, pneumonia or other non-specific chest infections), colds and other upper respiratory tract infections (URTIs) were recorded as counts. URTIs, other than colds, were defined as episodes of laryngitis, pharyngitis, sinusitis, tonsillitis, tracheitis, or other non-specific infections affecting the throat or trachea.

Measurement of adult socioeconomic position and lifestyle

Data on adult health and lifestyle were collected by self completion questionnaire at age 49-51 years. Current alcohol consumption was divided into four categories, based on average number of units consumed per week. Light drinking was defined as less than five units of alcohol per week for women (and ten for men) and moderate drinking as up to 21 units for women (and 28 for men). Current physical activity assessment was based on the Medical Research Council's national survey of health and development,[14] although the lowest category was partitioned to differentiate between low activity and zero activity individuals. Occupational details of the main wage earner in the household at age 49-51 were coded according to the 1990 UK Registrar General's Standard Occupational Classification and hence current social class was derived.

The number of pack-years of cigarettes smoked (one pack-year equals one pack of 20 cigarettes smoked per day for one year) was estimated from the study members' smoking habits at ages 15, 25, 35 and 50 years as recorded on the self-completion questionnaire at age 49-51. A variable for current smoking status (never, ex-smoker and current smoker) was also derived. We have previously shown that less than 2% of reported non-smokers had an exhaled carbon monoxide level of greater than 10ppm. [15] Occupational exposure to asbestos, dust or fumes was estimated by use of a job exposure matrix.[16] Individuals were placed into two groups, 'normal' and 'increased', according to their likelihood of exposure, where 'increased' included anyone who had ever been employed in an occupation with a 'high' likelihood of exposure for 'most' employees (according to the job exposure matrix). Use of beta-blockers was estimated from self reported current medication. Study members were also asked to report if they had ever been diagnosed with asthma, or if they had recently suffered from a lower respiratory tract infection. Self reported history of asthma was combined with any recorded childhood diagnoses, to maximise detection.

Statistical Analysis

Twins (n = 11) were excluded from all analyses. How representative the participants in this study were, in relation to the original cohort, was examined using a combination of T, Mann-Whitney and chi-squared tests, according to the characteristics of the data.

Social class at birth and in adulthood, housing conditions at birth, current smoking status, physical activity, and alcohol consumption were all treated as categorical variables. Relationships between FEV_1 and potential explanatory variables were estimated by linear regression. Unadjusted coefficients for each variable were determined to estimate the total influence of that variable on FEV_1. To estimate the direct influence of each variable (i.e. not mediated through other factors), an adjusted model was constructed using backwards stepwise regression. Height was included in the model as a quadratic term ($b_1$height + $b_2$height-squared) due to a non-linear relationship with FEV_1 (height-squared was transformed to have a mean of zero, to prevent co-linearity with height). The presence of heteroskedasticity was determined using the Cook-Weisberg test. Where necessary, Huber / White estimators of variance were used to provide robust p-values and confidence intervals. Potential interactions between significant variables in the adjusted model were examined within the linear regression models.

To estimate indirect pathways present within the adjusted model (i.e. non-independent predictors of FEV_1, which are mediated through other variables), it was reconstructed as a path diagram. In order to allow comparison between variables, and estimate relative importance, standardised beta coefficients (β) were derived for each explanatory variable (where a standardised coefficient is the standard deviation change in FEV_1 elicited by one standard deviation increase in an explanatory variable). Estimates, p-values, and confidence intervals were obtained by Monte-Carlo bootstrapping (50,000 repeats) of the maximum likelihood estimates.

All standard statistical analyses were performed using Stata 9.2 (StataCorp, College Station, USA), while AMOS 7.0 (SPSSInc, Chicago, USA) was used for the path analysis.

RESULTS

Of the original 1142 study members, 832 (89% of the surviving sample of 932 children whose families remained in Newcastle upon Tyne for at least the first year of the study) were traced at age 49-51 years.[17] Of these, 574 completed the health and lifestyle questionnaire, 412 attended the clinical examination, and 403 provided usable FEV_1 values, which after excluding 11 twins left a sample of 392. The study sample did not differ significantly ($p>0.05$) from the members of the original cohort not included in this analysis in terms of any of the factors around birth, infancy and childhood except for sex (women were more likely to attend the clinical examination then men ($p<0.001$).

Descriptive statistics for all variables are shown in tables 1 and 2 and the results of the regression analysis (including crude and adjusted regression coefficients) are shown in table 3. Male sex and greater height were significantly associated with higher FEV_1 ($p<0.001$). Although a substantial portion of the impact of sex was mediated through height ($p<0.001$), the associations were independent of each other. A prior diagnosis of asthma was associated with significantly lower adult FEV_1, both at univariate level ($p=0.006$), and after adjustment for other significant variables ($p=0.013$).

Fetal, infancy and childhood factors

More disadvantaged social class at birth was a significant unadjusted predictor of reduced FEV_1 ($p=0.031$). However, after adjustment for adult smoking status and body fat percentage it was no longer significant ($p=0.263$). While standardised birth weight was not a significant univariate predictor of adult FEV_1, it became significant after adjustment for sex and remained so in the fully adjusted model ($p=0.011$).

Of the childhood illness variables, only the number of LRTIs (between ages 0 and 5 years) showed a significant association with FEV_1 ($p=0.021$), which remained in the adjusted model. As a continuous variable, duration of breastfeeding showed no association with adult FEV_1 ($p=0.615$). However, when dichotomised at four weeks, individuals breastfed for less than four weeks had a significantly lower adult FEV_1 ($p=0.005$), that was not substantially altered in the adjusted model ($p=0.017$).

Adult factors

Current smokers had substantially lower FEV_1 values than never-smokers (adjusted $p<0.001$). An inverse association was seen between percent body fat and FEV_1 ($p<0.001$) and remained in the adjusted model ($p=0.010$). While physical activity, occupation, self reported LRTIs within the last three years and alcohol consumption were significant at the univariate level, they were not in the adjusted model. The associations of FEV_1 with each of occupational exposure and alcohol consumption were explained by the sex differences in their distributions (men were more likely to be employed in 'increased' exposure jobs, and more likely to drink larger quantities of alcohol) and FEV_1. The significant univariate association with self reported LRTIs within the last three years was lost after adjustment for asthma and cigarette smoking status. Rather than being accounted for by any one factor, the association between physical activity and FEV_1 was reduced only after simultaneous adjustment for sex, cigarette smoking, and body fat.

Relative importance

Figure 1 illustrates the adjusted model in schematic form, as estimated by path analysis. The standardised direct effect of each significant relationship is shown, as well as the standardised total effect of each variable (i.e. including both the direct effect and indirect effects mediated through other variables). Sex, which is both directly predictive of FEV_1, and indirectly associated through height, birth weight and body fat percentage, had the highest total effect [β=-0.626 (95% CI: -0.683, -0.563], while the effect of height was less than half the size [β=0.263 (95% CI: 0.159, 0.365)]; although conceptually, this should be combined with the value for height-squared [β=0.094 (95% CI: 0.021, 0.165)].

After sex and height, current smoking was the next largest predictor of adult FEV_1 [β=-0.178 (95% CI: -0.256, -0.100)]. The predictive total effects of birth weight and the number of childhood LRTIs were β=0.150 (95% CI: 0.076, 0.223) and β=-0.121 (95% CI: -0.195, -0.047) respectively, although, in both cases, nearly a third of the effect was mediated through achieved adult height. The impacts of asthma [β=-0.111 (95% CI: -0.184, -0.039)], percent body fat [β=-0.096 (95% CI: -0.172, -0.019)], and duration of breast feeding [β=0.089 (95% CI: -0.162, -0.018)] were of similar magnitude.

Interactions

No significant interactions were observed between sex and any other variable in the adjusted model. Of all other potential interactions, only birth weight and current smoking status were shown to be significantly interacting ($p=0.001$), with birth weight showing a greater association with FEV_1 among current smokers compared to never-smokers.

DISCUSSION

Principle findings

We have investigated lifecourse predictors of adult respiratory health using data from the Newcastle Thousand Families study. Sex, adult height, percent body fat, a history of asthma, current cigarette smoking status, standardised birth weight, history of childhood LRTIs, , and a short (less than four weeks) duration of being breast-feeding were all shown to be independently associated with FEV_1. Several indirect pathways including these variables were also identified, suggesting that some of their effects may be mediated through factors later in the lifecourse.

Strengths and weaknesses

The main strength of this study is that we were able to analyse data collected prospectively on early life experience alongside current indices of adult health and lifestyle. Unusually for this type of study, detailed and prospectively collected data were available on socioeconomic circumstances, infections, and feeding in early life. Measurements at age 49-51 included a direct estimate of percent body fat based on bioelectrical impedance, which, in contrast to body mass index, is largely independent of build.

Of 1142 people recruited at birth in 1947, 34% participated in this study, a favourable inclusion rate when compared to similar longitudinal studies,[8, 18]. Apart from sex, the study sample was comparable for all early life variables included in this study. Given that no interactions were observed between sex and any other significant variable, we can be confident that this did not bias the overall results. In addition, the inclusion of cohort members who had moved out of the study region increased the representativeness of the population studied. Unfortunately, the lack of modern reference values for FEV_1 for a typical general population (i.e. one that contains asthmatics and smokers), makes it difficult to compare this cohort to the general population in terms of respiratory function.

To account for possible occupation exposures, a job exposure matrix was used to estimate exposure to asbestos, dust, and fumes from retrospectively reported job titles. Data on the duration of employment in at risk jobs and details of the specific duties were not available. In combination with potential recall bias, it is unlikely that the occupational variable had sufficient power to detect any direct associations, but it is also unlikely to have confounded any of our results.

The use of path analysis imparts several benefits over standard linear regression, including a more illustrative quantification of the different pathways of influence. There are, however, certain limitations of the procedure that are important to note. Firstly, the direction of causal flow has to be inferred by the researcher. This should be less of an issue in this study, however, as the direction was usually indicated by the temporal relationships between the variables.

As with all forms of statistical modelling, path models are also susceptible to the nuances of the data from which they are constructed. It is therefore important to consider the characteristics of the cohort studied when estimating the relevance to other populations.[17]

A more specific limitation of path analysis is the sensitivity to error. Since effect sizes are estimated from standardised coefficients, and standardised coefficients are influenced by standard deviations, then any source of error has a potential impact on the relative effect-size. However, given that the majority of data included in this study were prospectively collected, then this issue is likely to be as small as is possible for this type of investigation.

Comparisons with other studies

Sex and height have long been known to dictate a large proportion of the natural variation in lung function, and are hence standard variables in prediction equations.[19, 20] More recently, it has been suggested that body fat should also be factored into these equations.[21] Our results confirm that body composition is predictive of adult FEV_1, although the effect was reduced substantially after adjustment for other factors.

The identified association between standardised birth weight and adult lung function provides further support for the ‘fetal programming’ hypothesis,[22] with partial mediation via adult height. The results of previous studies have been inconsistent, with a meta-analysis suggesting a small positive association.[2] Our results cannot be directly compared with this meta-analysis, since a standardised index of birth weight was used. However, when we substituted crude birth weight into the adjusted model, a coefficient of 0.134 (95% CI: 0.024, 0.245) was observed. Although this value is greater in magnitude than the meta-estimate [0.048 (95% CI: 0.026, 0.070)], the two values

are not significantly different (p=0.137). Nevertheless, it is important to note that the Thousand Families cohort was born when food rationing was still commonplace throughout the UK. It has been proposed that, during this time, the normal nutritional variation between UK social groups was attenuated.[23] This hypothesis appears to be supported by the lack of a socioeconomic gradient for birth weight in the Thousand Families cohort.[24]

In common with previous research,[3-8] this study demonstrated a direct linear association between increasing number of LRTIs during childhood, and reduced adult FEV_1. No relationship was observed between birth weight and childhood LRTIs, although some of the effect of LRTIs was mediated through achieved adult height. Unfortunately, this study does not help to clarify the direction of causality between childhood LRTIs and FEV_1. Indeed, early lung infections may simply be more likely in individuals with pre-existing respiratory problems.

In common with other studies.[25, 26], we identified a clear negative association between asthma and FEV_1. However, historically, childhood asthma was often diagnosed as 'wheezy bronchitis',[27] hence it is possible that under ascertainment has occurred. Neither whooping cough nor tuberculosis was associated with adult FEV_1. In the case of tuberculosis, this may have been due to low power. However, for whooping cough this is less likely to be the case, as 44% of the participants were diagnosed with whooping cough before the age of five years. Consistent with previous findings,[4-6, 28] childhood whooping cough does not appear to have a long-term impact on adult respiratory function

The impact of breast feeding on long term respiratory health has received relatively little attention. Although several studies have demonstrated better respiratory outcomes among children who have been breast fed,[29, 30] very few have investigated whether this trend continues into adulthood. One Canadian study of adults aged between 35 and 79, identified a lower FEV1 (albeit non-significantly) among those that had not been breast fed.[31] A more recent study found that FEV_1 was non-significantly lower among the individuals who had been breast fed for less than four weeks.[32] We found a similar trend, although in our data the effect was substantially larger (and statistically significant). However, no linear association was observed between the duration of breast feeding as a continuous variable and FEV_1. Further research is clearly required to explore the nature of this relationship.

In contrast to our findings, socio-economic status and physical activity have both previously been associated with FEV_1.[33, 34] This is potentially due to covariance with other factors, including body fat and cigarette smoking status. However, it is also possible that statistical power may have been an issue due to the low number of study members from the more advantaged childhood socio-economic groups and the relatively small number of moderate and highly active individuals.

Conclusion

Our study confirms that adult lung function is determined by a number of factors, acting both directly and indirectly throughout the lifecourse. Birth weight (standardised for sex and gestational age) and childhood LRTIs were both predictive of adult FEV_1. Despite the various significant effects reported, it is important to note that current smoking was the strongest individual predictor of adult FEV_1 after sex and height. Therefore, prevention and cessation of cigarette smoking should still be considered the primary intervention for improving respiratory health at a population level.

Table 1 Descriptive Statistics for Continuous Variables

		Men (N = 169)			Women (N = 223)		
Time Point	**Variable (Normally Distributed)**	**Range**	**Mean (SD)**	**n**	**Range**	**Mean (SD)**	**n**
Fetal	Birth weight[a] (Z-score)	-2.7 - 2.2	-0.3 (0.9)	169	-3.2 - 3.0	0.0 (1.1)	223
Adulthood	Body Fat (%)	15.4 - 54.4	36.3 (7.2)	168	14.4 - 61.8	41.7 (9.1)	219
General	Height (cm)	151.4 - 189.7	173.3 (6.5)	168	147.1 - 176.1	161.4 (6.0)	221
Time Point	**Variable (Not Normally Distributed)**	**Range**	**Median (IQR)**	**n**	**Range**	**Median (IQR)**	**n**
Childhood	Total colds between ages 0 - 5	0 - 13	3 (2 - 5)	168	0 - 12	3 (1 - 5)	222
	Total URTIs[b] between ages 0 - 5	0 - 11	1 (0 - 3)	168	0 - 10	2 (1 - 3)	222
	Total LRTIs[c] between ages 0 - 5	0 - 10	0 (0 - 1)	168	0 - 8	0 (0 - 1)	222
Adulthood	Cigarette smoking history (pack - years)[d]	0.1 - 73.0	22.6 (8.3 - 33.5)	110	0.1 - 40.5	17.2 (5.7 - 26.0)	120
Outcome	FEV_1[e] (Litres)	1.6 - 5.6	3.6 (3.2 - 3.9)	169	1.4 - 4.7	2.6 (2.3 - 2.9)	223

[a]Adjusted for sex and gestational age (Ref 13). [b]Upper Respiratory Tract Infections *excluding* colds. [c]Lower Respiratory Tract Infections.
[d]Excluding 56 men and 103 women who have never smoked. [e]Forced Expiratory Volume in 1st Second

Table 2 Descriptive Statistics for Categorical Variables

Time Point	Variable	Category	Men (N = 169) Number	Men (N = 169) Percent	Women (N = 223) Number	Women (N = 223) Percent
Fetal	Social class at birth[a]	I, II	21	12.8	19	8.6
		III	96	58.5	144	65.5
		IV, V	47	28.7	57	25.9
			(n = 164)		**(n = 220)**	
	Housing conditions at birth[b]	0	81	48.5	109	48.9
		1	37	22.2	60	26.9
		2	31	18.6	27	12.1
		≥ 3	18	10.8	27	12.1
			(n = 167)		**(n = 223)**	
Childhood	Had measles between ages 0 - 5	No	80	47.6	91	41.0
		Yes	88	52.4	131	59.0
			(n = 168)		**(n = 222)**	
	Had influenza between ages 0 - 5	No	158	94.1	218	98.2
		Yes	10	6.0	4	1.8
			(n = 168)		**(n = 222)**	
	Had whooping cough between ages 0 -	No	94	56.0	126	56.8
		Yes	74	44.1	96	43.2
			(n = 168)		**(n = 222)**	
	Had tuberculosis between ages 0 - 5	No	155	92.3	212	95.5
		Yes	13	7.7	10	4.5
			(n = 168)		**(n = 222)**	
	Breast fed for less than four weeks	No	133	79.6	156	71.9
		Yes	34	20.4	61	28.1
			(n = 167)		**(n = 217)**	
Adulthood	Social class at 49-51[a]	I, II	80	49.7	108	51.7
		III	63	39.1	69	33.0
		IV, V	18	11.2	21	15.3
			(n = 161)		**(n = 209)**	
	Cigarette smoking status[c]	None	56	33.7	103	46.2
		Ex	69	41.6	55	24.7
		Current	41	24.7	65	29.2
			(n = 166)		**(n = 223)**	
	Alcohol consumption[c]	None	11	6.6	32	14.5
		Light	65	38.9	91	41.2
		Moderate	71	42.5	87	39.4
		Heavy	20	12.0	11	5.0
			(n = 167)		**(n = 221)**	
	Physical activity[c]	None	13	7.8	32	14.4
		Low	92	55.4	104	46.9
		Medium	35	21.1	52	23.4
		High	26	15.7	34	15.3
			(n = 166)		**(n = 222)**	
	Occupational exposure[d]	Normal	110	65.1	221	99.1
		Increased	59	34.9	2	0.9
			(n = 169)		**(n = 223)**	
	Had LRTI[e] during ages 47 – 50[c]	No	149	89.8	184	82.9
		Yes	17	10.2	38	17.1
			(n = 166)		**(n = 222)**	
	Current beta-blocker usage	No	160	94.7	211	94.6
		Yes	9	5.3	12	5.4
			(n = 169)		**(n = 223)**	
General	Ever diagnosed with asthma[e]	No	147	88.0	194	87.0
		Yes	20	12.0	29	13.0
			(n = 167)		**(n = 223)**	

[a]As defined by the UK Registrar General's Standard Occupational Classification, where I is the most advantaged and V the least. [b]From none to three or more of: overcrowding, lack of hot water, shared toilet, and dampness or poor repair. [c]Self reported. [d]Ever employed in an occupation with an increased risk of exposure to asbestos, dust or fumes (Ref 16). [e]Self reported or abstracted from early records

Table 3 Results of regression analysis showing the coefficients for all variables on FEV_1. Adjusted coefficients are shown for variables included in the adjusted model.

Time Point	Variable	Category	Unadjusted Coefficient (95% CI)	p-value		Adjusted Coefficient (95% CI)	p-value	
Fetal	Social class at birth[a]	I, II	Reference		Total for variable:			
		III	-0.222 (-0.470, 0.025)	0.078				
		IV, V	-0.296 (-0.565, -0.027)	0.031	0.096			
	Housing conditions at birth[b]	0	Reference		Total for variable:			
		1	-0.133 (-0.316, 0.051)	0.156				
		2	-0.050 (-0.271, 0.170)	0.652	0.506			
		≥ 3	-0.110 (-0.353, 0.133)	0.375				
	Standardised birth weight[c] (z-score)		0.047 (-0.024, 0.118)	0.191		0.067 (0.016, 0.119)	0.011	
Childhood	Had measles between ages 0 - 5	No	Reference					
		Yes	-0.129 (-0.278, 0.020)	0.090				
	Had influenza between ages 0 - 5	No	Reference					
		Yes	0.188 (-0.211, 0.586)	0.355				
	Had whooping cough between ages 0 - 5	No	Reference					
		Yes	-0.053 (-0.202, 0.097)	0.487				
	Had Tuberculosis between ages 0 - 5	No	Reference					
		Yes	0.004 (-0.311, 0.319)	0.979				
	Breast fed for less than four weeks	No	Reference			Reference		
		Yes	-0.245 (-0.416, -0.074)	0.005		-0.148 (-0.269, -0.027)	0.017	
	Total colds during ages 0 - 5		0.013 (-0.014, 0.041)	0.347				
	Total URTIs[d] during ages 0 - 5		-0.026 (-0.064, 0.012)	0.183				
	Total LRTIs[e] during ages 0 - 5		-0.072 (-0.133, -0.011)	0.021		-0.049 (-0.088, -0.009)	0.015	
Adulthood	Social class at 49-51[a]	I, II	Reference		Total for variable:			
		III	-0.124 (-0.287, 0.039)	0.135				
		IV, V	-0.178 (-0.407, 0.050)	0.125	0.168			
	Cigarette smoking status[f]	None	Reference		Total for variable:	Reference		Total for variable:
		Ex	0.113 (-0.056, 0.282)	0.188		-0.061 (-0.177, 0.056)	0.306	
		Current	-0.309 (-0.486, -0.132)	0.001	< 0.001	-0.288 (-0.421, -0.154)	< 0.001	< 0.001
	Alcohol consumption[f]	None	Reference		Total for variable:			
		Light	0.282 (0.031, 0.534)	0.028				
		Moderate	0.331 (0.080, 0.583)	0.010	0.077			
		Heavy	0.304 (-0.040, 0.648)	0.084				
	Physical activity[f]	None	Reference		Total for variable:			
		Low	0.388 (0.152, 0.624)	0.001				
		Medium	0.447 (0.185, 0.709)	0.001	0.004			
		High	0.438 (0.157, 0.719)	0.002				
	Occupational exposure[g]	Normal	Reference					
		Increased	0.698 (0.506, 0.890)	< 0.001				
	Had LRTI[e] during last three years[f]	No	Reference					
		Yes	-0.301 (-0.513, -0.089)	0.005				
	Current beta-blocker usage	No	Reference					
		Yes	-0.178 (-0.506, 0.150)	0.287				
	Cigarette smoking history (pack - years)		-0.002 (-0.007, 0.003)	0.515				
	Body fat (%)		-0.025 (-0.033, -0.017)	< 0.001		-0.008 (-0.014, -0.002)	0.010	
General	Sex	Male	Reference			Reference		
		Female	-0.951 (-1.071, -0.830)	< 0.001		-0.609 (-0.763, -0.455)	< 0.001	
	Ever diagnosed with asthma[h]	No	Reference			Reference		
		Yes	-0.313 (-0.534, -0.091)	0.006		-0.199 (-0.356, -0.041)	0.013	
	Height (cm)		0.054 (0.047, 0.061)	< 0.001		0.022 (0.012, 0.032)	< 0.001	
	Height^2 ($cm^2 \times 10^3$) (difference from mean)		1.321 (0.332, 2.310)	0.009		0.758 (0.026, 1.491)	0.043	

[a]As defined by the UK Registrar General's Standard Occupational Classification, where I is the most advantaged. [b]From none to three or more of: overcrowding, lack of hot water, shared toilet, and dampness or poor repair. [c]Adjusted for sex and gestational age (Ref 13). [d]Upper respiratory tract infections *excluding* colds. [e]Lower respiratory tract infections. [f]Self reported. [g]Ever employed in an occupation with an increased risk of exposure to asbestos, dust or fumes (Ref 16) [h]Self reported or abstracted from early records.

FIGURE LEGENDS

Figure 1 Path diagram of the adjusted regression model, showing predictors of FEV_1. Direct effects are represented by solid arrows and are labelled with standardised coefficients (β). Intermediate associations between independent variables are represented by dotted arrows, with the arrow direction indicating the hypothesised direction of causal flow. Indirect effects are any pathways that are mediated through at least one intermediate (e.g. Sex » Body Fat » FEV_1). The standardised total effect for each variable is the sum of the direct and the indirect effects, and the value is shown underneath the variable name. Error terms, covariance between error terms and relationships with height-squared are omitted for simplicity.

ACKNOWLEDGEMENTS

We thank the Thousand Family Study members for taking part, the study teams past and present, and Newcastle Healthcare Charity for providing funding for the analysis. We also thank Professor David Coggon for supplying the Job Exposure Matrix and advising on its use.

COMPETING INTERESTS

None declared

FUNDING

This analysis was funded by the Newcastle Healthcare Charity.

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Figure 1