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The association of birth weight with adult lung function: findings from the British Women's Heart and Health Study and a meta-analysis.

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Abstract

Background The aim of this study was to examine the associations between birth weight and lung function in a cohort of women aged 60-79 and to combine these results with those from other published studies in a systematic review and meta-analysis.

Methods The associations of self-reported birth weight with adult lung function (forced expiratory volume in one second (FEV_1), forced vital capacity (FVC) and forced expiratory flow rate during mid-expiration (FEF_{25-75}), all measured using standard procedures, were assessed in a cross-sectional study of 2,257 British women aged 60-79 years. A detailed literature search was used to identify all published studies of the association, and meta-analysis was used to pool the results from our study and all published studies.

Results There were positive linear associations between birth weight and all three measures of lung function in simple age and examining nurse adjusted regression models. However, with adjustment for height (squared) all three associations attenuated towards the null: adjusted (age, nurse, height^2) change in FEV_1 per 1kg birth weight was 0.01 l (95% CI: -0.02, 0.04 l); in FVC was 0.02 l (95% CI: -0.02, 0.07 l) and in FEF_{25-75} was 0.00 l (95% CI: -0.04, 0.04 l). Further adjustment for life course socioeconomic position, adult body mass index and smoking status did not alter these associations. Results were similar among life long non-smokers and those who had ever smoked. A meta-analysis of 8 studies of adults suggested that there was a positive association between birth weight and FEV_1: pooled increase in FEV_1 per 1kg in birth weight 0.048 l (0.026, 0.070 l) adjusted for age, smoking and height (or height^2). There was no evidence of small study bias in this meta-analysis.

Conclusions We have found a modest positive association between birth weight and lung function, which indicates that intrauterine factors might have a role in lung development.

Key words: Birth weight; Foetal origins; Life course epidemiology; Lung function

Introduction

Poor lung function in adulthood is associated with increased risk of cardiovascular disease and all-cause mortality even among life long non-smokers, but the explanation for these associations are unclear.[1 2 3] It is possible that they reflect early life exposures that influence lung growth and development as well as adult disease risk. The foetal origins hypothesis proposes that the foetus adapts its growth rate as a response to changes in nutrient and oxygen supply. These adaptations affect growing organs and hormonal and metabolic pathways.[4] Thus a reduced supply of nutrients to the foetus may result in low birth weight and, depending upon the timing, may result in specific detrimental effects to growing organs such as the liver, pancreas, heart and lungs.[4 5] Birth weight has been shown to be inversely associated with cardiovascular disease risk and this association is independent of socioeconomic position, a range of cardiovascular risk factors and adult body size.[4 6] The association between poor lung function and cardiovascular disease may, in part, be related to intrauterine factors that affect foetal growth, programme cardiovascular disease and also affect lung growth and development.[5]

Several studies have examined the association between birth weight and lung function, with some,[7 8 9 10 11] though not all,[12 13 14 15 16] finding a positive association. These conflicting results may be due to the small sample sizes of most studies and differences between studies in the range of potential confounding factors that were taken into account. Importantly several of the studies did not control for childhood socioeconomic position,[9 10 12 13 14] despite this being strongly related to both birth weight[17] and lung function.[18] Whilst most studies adjusted in multivariable models for adult smoking status, because of the very strong association between smoking and lung function stratified analyses would provide better evidence that any association was not largely explained by smoking. Finally, it has been suggested that the inverse association is largely due to poor lung function in very low birth weight infants and that the results of some studies claiming an inverse association across the birth weight distribution are largely driven by the effect in very low birth weight infants.[13]

The aim of this study was to examine the associations between birth weight and lung function in a cohort of over 2200 women aged 60-79 and to combine these results with those from other published studies in a systematic review and meta-analysis in order to obtain a precise estimate of the strength of association between birth weight and lung function.

Methods

Participants

Data from the British Women's Heart and Health Study were used. Full details of the selection of participants and measurements used in the study have been previously reported.[18 19] Between 1999 and 2001 4,286 women aged 60 to 79 years, who were randomly selected from 23 British towns were interviewed, examined, completed medical questionnaires and had detailed reviews of their medical records. These women have been followed-up over a median of 4 years by flagging with the NHS central register for mortality data, two yearly review of their medical records and a mailed 3-year follow up health questionnaire (Q3) sent to all surviving participants between March and September 2003. Of the 4,108 survivors, 3704 (90%) responded to this questionnaire. Local ethics committees' approvals were obtained for the study.

Measurements

Lung function tests

Lung function tests were carried out with a digital meter Vitalograph with an attached printout of forced vital capacity (FVC), forced expiratory volume in one second (FEV_1) and forced mid-expiratory flow rate (FEF_{25-75}). The Vitalograph was calibrated each day using a 1 litre syringe and automated so that results were adjusted for ambient temperature. For each assessment a research nurse demonstrated the technique to the participant. The participants then performed some practice efforts. They were then required to perform a minimum of three reproducible FVC measures (within 5% of maximum FVC produced). The output that produced the highest sum of FVC and FEV_1 were used in the analyses. Women who could not perform three reproducible measures or who were unable to attempt the lung function assessment were excluded. All assessments were carried out by one of five research nurses who were trained to carry out the assessment in a similar manner.

Birth weight

In both the baseline questionnaire and Q3 women were asked to record their birth weight in pounds and ounces, which were converted to kilograms. In Q3 only, women were also asked to indicate which of five birth weight categories (of 2 lb size) they believed their birth weight fell in to. In previous publications we have demonstrated that self-reported birth weight at baseline had a similar distribution to British women of a similar age for whom there were hospital records of birth weight available and that the associations between self-reported birth weight at baseline and adult anthropometric measures were in the same direction and of a similar magnitude to what would be predicted from recorded measures.[20 21] For those women who provided birth weights, rather than category of birth weight, at both baseline and Q3 (N=690) the two measures were highly correlated (Pearson's correlation coefficient 0.97), with a mean difference between the two measures (95% limits of agreement) of 0.013 (-0.379, +0.405) kg. For those women who also indicated which birth weight category they fell into (N=670) all but 12 showed absolute consistency between these two means of asking about birth weight. For this analysis a continuous birth weight variable has been generated for all women by using primarily the baseline self-report, substituting this for the Q3 continuous self-report if there were no baseline report and then substituting for the mid-point of the categorical values for those with no continuous report (N=853 of 2431 with any birth weight data). The mean birth weights for those providing a continuous value was identical to that calculated for those providing just a categorical value 3.30 (0.84) versus 3.31 (0.55).

Other measurements

As previously reported information on ten indicators of life course socioeconomic position were obtained from the baseline questionnaire: occupational social class of their father (categorised into 6 categories using the Registrar General's classification – I (professional) through to V (unskilled manual)); whether childhood home had a bathroom; whether childhood home had a hot water supply; whether participant shared a bedroom as a child; family access to a car when participant was a child; age at leaving full-time education (collapsed into 4 categories: < 15 years, 15-17 years, 18-21 years, > 21 years); adult occupational social class of head of household (categorised into 6 categories using the Registrar General's classification – I (professional) through to V (unskilled manual)); car access in adulthood; pension arrangements (state only, occupational and state, private and state, all three of occupational, private and state); house ownership (owner occupied, private renting, living with family, council (public) rented).[18]

Smoking history (never, past and current including amount and details of starting and quitting), marital status and husbands'/long-term partners' smoking history (never, past and current including amount and details of starting and quitting) were self-reported either at the research nurse interview or in the mailed questionnaires. Standing height was measured, without shoes, using a Harpenden Stadiometer recording to the nearest millimetre and weight (to nearest 0.5kg) was measured in light clothing using a Schoen portable scale that was calibrated each morning.

Statistical Analysis

Analysis of variance was used to assess between nurse variation in lung function measurements. A series of linear regression models were used to estimate the association between birth weight and each measure of lung function. In the basic models adjustment was made for examining nurse and age. In the next model height squared was added to the basic model. The square of height was used because in an earlier study of the association between stature and lung function it was concluded that a proportional model best described the association[22] and in our data we found that this was also the case (in a regression model with height this explained 12% of the variation in FEV_1 whereas height squared explained 17%). Additional adjustment was then made for all indicators of socioeconomic position from across the life course and in the final model the women's adult smoking status was also added. In order to determine whether the association was linear we first examined the association with three indicator variables for the quarters of birth weight and then compared this to a model in which the birth weight quarters were entered as a continuous variable. We computed a likelihood ratio test to compare these two nested models. In addition we examined the association in a restricted sample of women excluding those in the lowest quarter of the birth weight distribution and who may have had low birth weight because of prematurity. To determine whether there was any interaction between birth weight and either adult height or adult body mass index all of these variables were split into quarters and stratum specific associations examined. F-tests were computed to determine statistical evidence of an interaction between birth weight and adult anthropometric measurements in their associations with lung function. Because of the strong association between adult smoking and lung function simple adjustment for smoking in regression models may be insufficient to account for its potential confounding effects. As a result the regression models were repeated stratified by smoking status. In all analyses robust confidence intervals were estimated which take into account the clustering between participants from the same towns.

To correct for the possibility that our estimates of the association between birth weight and lung function would be diluted by our use of self-reported birth weight we undertook a series of sensitivity analyses in which we used the reported correlation coefficients of the association between self-report and medical records of birth weight to correct our estimate.[23] In these analyses we used intraclass correlations of 0.6 and 0.9 to correct our regression coefficients.[23] All analyses were undertaken using Stata version 8.

Meta-analysis
A search of Medline and Embase (up to December 2004) was undertaken using the search terms: [‘lung function’ OR ‘FEV$’ OR ‘FVC$’ OR ‘FEF$’ OR ‘Spirometr$’] AND [‘birth weight’ OR ‘birth size’ OR ‘intrauterine growth’ OR ‘small for gestational age’ OR ‘fetal origins$’ OR ‘Barker’s hypothesis’]. Bibliographies were searched for additional references. Studies were included in the systematic review if they examined the association between birth weight and lung function assessed in adulthood (defined as age 18 years or older). We included studies that were written in any language. Studies were included in the meta-analysis if a regression coefficient of the association of measures of FEV_1 on birth weight were presented, could be estimated or was obtained through contact with the authors. Meta-analyses of other lung function outcomes were not undertaken because there were too few studies with outcomes other than FEV_1. We decided *a priori* to assume heterogeneity between studies as some studies were in male populations only and our study was in a female population. Foetal growth rates differ between the sexes and in other areas it has been suggested that this results in different effects of foetal programming between the sexes.[24] Therefore random effects meta-analysis was undertaken.[25] Funnel plots were examined and statistical evidence of small study bias was assessed with Egger and Begg tests.[25] All analyses were undertaken using Stata version 8.

Results
Of the 4,286 participants 3,911 (91%) completed adequate lung function measures and 2,431 (57%) provided self-reported data on their birth weight. Those who were unable to complete adequate lung function measures were older (mean age (SD) 69.8 (5.7) years versus 68.8 (5.5) years, p = 0.001) and more likely to have ever been smokers (61.7% (56.6, 66.6%) versus 53.5% (52.0, 55.1%), p = 0.003). Women who provided self-reported data on birth weight had better lung function tests to those who did not (mean (SD) values in those with birth data compared to those without these data were: 2.02 (0.5) l versus 1.19 (0.5) l, p < 0.001 for FEV_1; 2.86 (0.8) l versus 2.73 (0.7) l, p < 0.001 for FVC and 1.50 (0.7) l versus 1.37 (0.7) l, p < 0.001 for FEF_{25-75}). Women who provided birth weights were also less likely to be from manual social classes in childhood (77.2% versus 83.7%, p < 0.001) and adulthood (54.8% versus 60.6%, p < 0.001), were less likely to be current smokers (10.6% versus 13.0%, p = 0.02) and were taller as adults (1591.4mm versus 1582.9mm, p <0.001). There was evidence of some difference between the nurses in lung function assessments: mean FEV_1 (SD) for nurse 1 was 2.00 (0.53) l; for nurse 2 was 1.92 (0.46) l; for nurse 3 was 2.02 (0.52) l; for nurse 4 was 2.01 (0.50) l; and for nurse 5 was 1.96 (0.50) l, p (analysis of variance for difference in means) = 0.05. All lung function measures have therefore been adjusted for examining nurse, by including examining nurse as an indicator variable in all analyses. In total 2,257 (53%) of women had complete data on both lung function measures and birth weight and all remaining analyses are for these 2,257 women only. Birth weight was similar in those women who were able to perform lung function tests and those who were not (3.31kg versus 3.32kg, p = 0.4). Among the 2,257 women included in further analyses the mean (SD) birth weight was 3.31 (0.76) kg.

Tables 1 to 3 show the associations between birth weight and each measure of lung function. In the basic model with adjustment for examining nurse and age only, birth weight was positively and linearly associated with all three measures of lung function.

These associations were linear across the birth weight distribution and not simply driven by low function in those of very low birth weight. However, all of these associations attenuated towards the null with adjustment for the square of height. Further adjustment for life course socioeconomic position and adult body mass index and smoking did not substantially alter the height adjusted coefficients. There was no evidence of non-linear associations (all p-values > 0.4) and associations were similar among women reporting their birth weights in the lowest quarter of the distribution to those in all other women. There was no evidence of any interactions between birth weight and either adult height or body mass index in their associations with the different lung function measurements (all p-values > 0.6).

Sensitivity analyses

Using an intraclass correlation coefficient of 0.6 to correct for attenuation by errors, the associations of birth weight with lung function strengthened, but remained non-significant in the fully adjusted models. The corrected fully adjusted change in FEV_1 for a 1kg increase in birth weight was 0.02 (95% CI: -0.01, 0.03) l and the fully adjusted change in FVC was 0.03 (95% CI: -0.01, 0.06). The results were unaltered from those presented in tables 1-3 using an intraclass correlation coefficient of 0.9.

Smoking status was strongly associated with lung function. For example FEV_1 was 0.11 l (95%CI: -0.15, -0.07 l) lower among women who were past smokers compared to never smokers and was 0.38 l (95%CI: -0.45, -0.32 l) lower in current compared to never smokers in age, leg-length (squared), adult and childhood social class, birth weight and body mass index adjusted analyses. When the analyses were repeated in strata according to smoking status they were similar in women who were life-long non-smokers and either single or married to non-smokers and all other women. For example, the simple age and examining nurse adjusted change in FEV_1 per 1kg increase in birth weight among life long non-smokers (N=1272) was 0.08 (95% CI: 0.04, 0.11) l, p <0.001 and with additional adjustment for height squared this attenuated to 0.02 (95% CI: -0.01, 0.05) l, p = 0.27.

Meta-analysis

Ten studies[7 9 10 11 13 14 15 16 26 27] of the association between birth weight and lung function among adults were identified and these are summarised in Table 4. Regression coefficients of the association of FEV_1 on birth weight were either presented or obtained from investigators for 7 of these studies. When the results from these 7 studies were pooled with the results form the British Women's Heart and Health study there was a positive association between birth weight and FEV_1 adjusted for age, smoking and height (or height squared) at the time of lung function measurement, with FEV_1 increasing by 0.048 l (95%CI: 0.026, 0.070 l) for each increase of 1kg birth weight (Figure 1). Other covariates, as described in Table 4, had also been adjusted for in some studies, but because there was variation between studies in which of these individual covariates were taken into account we only pooled the age, smoking and height adjusted associations. There was weak statistical evidence of heterogeneity between these studies (p = 0.07). There was no evidence of small study bias (p=0.1 for Egger test and p = 0.2 for Begg's test). Of the three studies for which regression coefficients could not be obtained, one found no evidence of an association between birth weight and lung function,[13] whereas the other two found a positive linear association.[10 27]

Discussion

We found no association between self-reported birth weight and measures of lung function at age 60-79 years among over 2,000 British women once height was taken into account. Despite being one of the largest studies to date to assess the association between birth weight and lung function in adulthood, our results were imprecise and a meta-analysis suggested a positive association between birth weight and FEV_1. Exclusion of the three studies for which regression coefficients could not be obtained would be unlikely to make a major difference to this modest effect as they also showed only small effects and would have contributed about 15 % to the weight of the meta-analysis. We considered whether the lack of adjustment for socioeconomic position in previous studies might have influenced their results. However, in the British Women's Heart and Health study further adjustment for a range of life course socioeconomic indicators, once adult height had been taken into account, did not alter the regression coefficient, suggesting that socioeconomic position is not a major confounder in this association. All of the regression coefficients included in our meta-analysis had been adjusted for height prior to pooling. Thus, despite the modest association between birth weight and adult height (Pearson's correlation coefficient in the region of 0.2-0.3 in this and other studies[28 29]), the effect of birth weight on adult lung function is independent of adult height.

Study limitations

Our response (60%) is moderate but consistent with other contemporary large epidemiological surveys.[30] As reported previously participants were slightly younger than non-participants and less likely to have a primary care medical record of stroke or diabetes, though the prevalence of coronary heart disease and cancer did not vary between participants and non-participants.[19] The associations presented here would be exaggerated if they were in the opposite direction or markedly weaker among non-participants. Our study is cross-sectional. However, since the temporal nature of the association between birth weight and adult lung function is clear, reverse causality cannot explain our findings. An important limitation was the use of self-reported birth weight, and the fact that just 53% of the original cohort had data on birth weight and lung function tests. In previous studies we have demonstrated that recalled birth weight in the British Women's Heart and Health Study is associated with adult anthropometric measurements in the ways one would expect and the distribution of recalled birth weights in this cohort were similar to those of recorded weights for women of a similar age in the Hertfordshire cohort and the 1946 British birth cohort.[20 21] The mean self-reported birth weight of women in our study was 3.31kg (SD 0.76) which is consistent with hospital records of women born between 1923 and 1930 in Hertfordshire (3.42 kg, SD not provided)[31] and also with women in the 1946 British birth cohort (3.32 kg, SD 0.49 – personal communication from Professor D Kuh, University College London). Participants who provided birth weight data in our study had better lung function, were from more affluent social groups, were taller and were less likely to be current smokers, compared to those who did not provide birth weight data. However, inclusion of these variables in the regression models should yield unbiased estimates. In a number of studies self-reported birth weight has been found to correlate well with hospital records (correlation coefficients in the range of 0.64 to 0.86), though absolute levels of accuracy may be poor.[23] It is difficult to see how objective measurements such as lung function could influence birth weight recall, and therefore misclassification is likely to be non-differential and may, as a result, have diluted the associations. Our null results may, therefore, reflect the use of self-reported birth weight.

Foetal origins of adult lung function

We identified ten reports of the association between birth weight and lung function measured in adulthood, six of which reported a positive association between birth weight and lung function adjusted for age, height and smoking[7 8 9 10 26 27] and four of which, like our study, reported a null association.[12 13 14 15] In reality, as figure 1 demonstrates there is little heterogeneity between the studies with most demonstrating weak positive, but imprecise, associations between birth weight and FEV_1. Our study is in women only and there is some suggestion from figure 1 that our results differ from other studies in being closer to the null value (though there was no strong statistical evidence to support this). A weaker effect in our study compared to other studies could be due to the effect of non-differential bias resulting from our use of self-reported birth weight as discussed above, but in the Caerphilly study[26] of men self-report of birth weight in adulthood was also used and yet this study found a more positive association than that found in our study. Other studies included both sexes or were of men only. Thus, the weaker effect in our study may be explained by a weaker effect of birth weight on adult lung function in women compared to men. Foetal growth rates differ between the sexes, and in other areas it has been suggested that this results in different effects of foetal programming between the sexes.[24] Just one study presented results stratified by sex (Figure 1) and there was no evidence from this study that the effect of birth weight on FEV_1 differed between women and men.[9]

The magnitude of effect in individual studies and when these studies are pooled is modest. A 1 kg difference in birth weight is large and would be very difficult to obtain by modification of any known environmental risk factors and yet this large difference in birth weight was associated with just a 0.05 l difference in FEV_1 in the pooled analysis. This compares to the difference of -0.38 l comparing women who were current smokers to those who had never smoked in the British Women's Heart and Health Study. However, whereas current smoking will have a direct effect on lung function birth weight *per se* is unlikely to have a direct effect on adult lung function. Birth weight in these analyses is acting as a proxy marker for some other (environmental or genetic) exposure that influences birth size and has a lasting effect on adult lung function. Whilst genetic factors are important determinants of birth size, and heritability studies suggest that there are important genetic determinants of adult lung function that are independent of atopic disease, cigarette smoking, height, age or sex,[32 33 34] we are unaware of any candidate genes that are related both to birth weight and lung function and that could therefore explain their association.

Lung function increases in healthy children reaching a maximum in late adolescence / early twenties, stays at this level throughout adulthood and then begins to decline with age in late adulthood.[35] Intrauterine exposures could affect this normal trajectory in a number of different ways. Exposures that result in retarded foetal growth may irrecoverably constrain the growth of an individual's airways and result in poorer lung function that persists into adulthood.[5] In this scenario a low birth weight individual would have a similar pattern of lung development across their life course but would tend to have poorer lung function at any age compared to a normal birth weight individual. Maternal smoking during pregnancy and maternal nutrition across her life course and during pregnancy may be important factors affecting foetal growth and lung development.[5] All of the studies included in our meta-analysis had adjusted for participant smoking, but only one had adjusted for maternal smoking during pregnancy.[36] Maternal smoking during pregnancy is a strong determinant of birth weight[37] and could affect adult lung function via two pathways. First, maternal smoking is strongly related to offspring smoking,[38] which will have a direct effect on their lung function. If this were the only pathway through which maternal smoking affected adult lung function then adjustment for the more proximal 'own smoking' would adequately account for the effect of maternal smoking. However, there is evidence that maternal smoking during pregnancy has a direct effect on offspring lung development and lung function, irrespective of whether the offspring smokes,[36 39] providing a mechanism by which maternal smoking during pregnancy might influence adult lung function in their offspring. Independence of the effects of maternal smoking during pregnancy from birth weight on adult lung function was demonstrated by Boezen et al.[36] but it is impossible from the results presented to determine the extent of attenuation of the birth weight association with adjustment for maternal smoking. If maternal smoking is an important influence, our null findings might be explained by the relatively older age of our participants compared with other studies, which were of younger women, since female smoking rates were extremely low in Britain in the 1920s and 30s (with less than 0.1% of females in the 20-40 year age range smoking during these times[40]). Thus, in our study exposure to smoking during pregnancy simply did not arise for the vast majority of offspring and consequently could not provide a link between birth weight and adult lung function.

Post-natal factors, such as acute respiratory infections, might also affect lung growth and development differentially in low and normal birth weight infants, resulting in a slower increase in function during childhood and a lower adult plateau. Since respiratory infections are more common in those of low birth weight this might provide another mechanism linking low birth weight to poorer lung function in later adulthood. Some support for this hypothesis is provided by one study in which adjustment for childhood respiratory infections attenuated the birth weight-adult lung function association towards the null.[15]

One way to further explore the effect of intrauterine factors on lung development trajectories across the life course would be to examine the relationship of birth weight with repeated measurements of lung function taken within the same cohort across their life course. We are unaware of any study with repeated measurements of lung function that could determine whether the effect of birth weight varies with age.

To conclude, our results suggest that birth weight is positively associated with lung function in adulthood, the effect is small but does add to the evidence of a role of intrauterine factors in lung growth and development.

What this paper adds

Previous studies of the association between birth weight and lung function have been small and produced imprecise estimates. Our results from a large cohort of women and a meta-analysis suggest that there is a modest positive association between birth weight and forced expiratory volume in one second and support a role for intrauterine factors in lung development.

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Table 1: Multivariable associations of birth weight with FEV_1

	Difference (95% confidence interval) FEV_1 (l)			
	Model1[a]	Model 2[b]	Model 3[c]	Model 4[d]
Lowest quarter birth weight, range: 739-2826g N = 746	reference	reference	reference	reference
2nd quarter birth weight, range: 2872-3352g N = 476	0.07 (0.00, 0.13)	0.01 (-0.05, 0.07)	-0.01 (-0.07, 0.05)	-0.01 (-0.07, 0.05)
3rd quarter birth weight, range: 3353-3735g N = 774	0.11 (0.05, 0.15)	0.02 (-0.03, 0.08)	0.02 (-0.03, 0.07)	0.02 (-0.03, 0.07)
Highest quarter birth weight, range: 3736-5909g N = 435	0.13 (0.06, 0.19)	0.01 (-0.06, 0.07)	0.00 (-0.06, 0.06)	0.00 (-0.07, 0.06)
Per 1 kg birth weight	0.07 (0.04, 0.10)	0.01 (-0.02, 0.04)	0.01 (-0.02, 0.04)	0.01 (-0.02, 0.04)
p linear trend	< 0.001	0.48	0.47	0.42
p non-linear association	0.43	0.27	0.55	0.69
Per 1 kg excluding those in lowest birth weight quarter	0.04 (-0.02, 0.09)	0.00 (-0.05, 0.05)	0.00 (-0.05, 0.05)	0.01 (-0.04, 0.06)

FEV_1: forced expiratory volume in 1 second
[a] Model 1: adjusted for age and examining nurse
[b] Model 2: adjusted for age, examining nurse and height squared
[c] Model 3: adjusted for age, examining nurse, height squared, father's occupational social class, whether childhood house had a bathroom, whether childhood house had hot water, family access to a car in childhood, whether the participant shared a bedroom as a child, age at leaving full time education, adult occupational social class, adult car access, adult home ownership, pension arrangements
[d] Model 4: adjusted for all factors in model 3 and adult smoking

Table 2: Multivariable associations of birth weight with FVC

	Difference (95% confidence interval) FVC (l)			
	Model1[a]	Model 2[b]	Model 3[c]	Model 4[d]
Lowest quarter birth weight, range: 739-2826g N = 746	reference	reference	reference	reference
2nd quarter birth weight, range: 2872-3352g N = 476	0.15 (0.04, 0.26)	0.07 (-0.04, 0.17)	0.04 (-0.06, 0.15)	0.04 (-0.06, 0.14)
3rd quarter birth weight, range: 3353-3735g N = 774	0.18 (0.09, 0.27)	0.06 (-0.03, 0.17)	0.06 (-0.03, 0.15)	0.06 (-0.03, 0.15)
Highest quarter birth weight, range: 3736-5909g N = 435	0.19 (0.08, 0.30)	0.02 (-0.08, 0.13)	0.01 (-0.09, 0.12)	0.02 (-0.09, 0.12)
Per 1 kg birth weight	0.10 (0.05, 0.15)	0.02 (-0.03, 0.07)	0.02 (-0.03, 0.07)	0.02 (-0.02, 0.07)
p linear trend	< 0.001	0.42	0.41	0.31
p non-linear association	0.24	0.19	0.35	0.34
Per 1 kg excluding those in lowest birth weight quarter	0.02 (-0.07, 0.11)	-0.04 (-0.13, 0.05)	-0.02 (-0.11, 0.07)	-0.01 (-0.10, 0.08)

FEV_1: forced expiratory volume in 1 second
[a] Model 1: adjusted for age and examining nurse
[b] Model 2: adjusted for age, examining nurse and height squared
[c] Model 3: adjusted for age, examining nurse, height squared, father's occupational social class, whether childhood house had a bathroom, whether childhood house had hot water, family access to a car in childhood, whether the participant shared a bedroom as a child, age at leaving full time education, adult occupational social class, adult car access, adult home ownership, pension arrangements
[d] Model 4: adjusted for all factors in model 3 and adult smoking

Table 3: Multivariable associations of birth weight with FEF_{25-75}

	Difference (95% confidence interval) FEF_{25-75} (l)			
	Model1[a]	Model 2[b]	Model 3[c]	Model 4[d]
Lowest quarter birth weight, range: 739-2826g N = 746	reference	reference	reference	reference
2nd quarter birth weight, range: 2872-3352g N = 476	0.05 (-0.04, 0.14)	0.01 (-0.08, 0.10)	-0.01 (-0.10, 0.08)	-0.01 (-0.10, 0.08)
3rd quarter birth weight, range: 3353-3735g N = 774	0.07 (-0.01, 0.15)	0.01 (-0.07, 0.09)	0.01 (-0.07, 0.09)	0.00 (-0.08, 0.08)
Highest quarter birth weight, range: 3736-5909g N = 435	0.08 (-0.01, 0.18)	0.00 (-0.09, 0.10)	-0.01 (-0.11, 0.08)	-0.02 (-0.12, 0.07)
Per 1 kg birth weight	0.05 (0.01, 0.09)	0.01 (-0.03, 0.05)	0.01 (-0.04, 0.05)	0.00 (-0.04, 0.04)
p linear trend	0.03	0.67	0.78	0.88
p non-linear association	0.91	0.94	0.99	0.98
Per 1 kg excluding those in lowest birth weight quarter	0.04 (-0.04, 0.11)	0.01 (-0.06, 0.08)	0.01 (-0.07, 0.08)	0.01 (-0.07, 0.08)

FEV_1: forced expiratory volume in 1 second

[a] Model 1: adjusted for age and examining nurse

[b] Model 2: adjusted for age, examining nurse and height squared

[c] Model 3: adjusted for age, examining nurse, height squared, father's occupational social class, whether childhood house had a bathroom, whether childhood house had hot water, family access to a car in childhood, whether the participant shared a bedroom as a child, age at leaving full time education, adult occupational social class, adult car access, adult home ownership, pension arrangements

[d] Model 4: adjusted for all factors in model 3 and adult smoking

Table 4: Summary of published studies examining the association between birth weight and lung function

First author (year publication)	Study type	N	Country	Age at lung function tests	Source birth weight data	Main results (As published)	Beta-coefficient (SE) [L/kg] used in meta-analysis*	Controlled for:
Barker (1991)	Retrospective cohort	825	England	59-70	Obstetric records	Change per 1lb birth weight: FEV_1: 0.06 (0.02, 0.09) l	0.03 (0.014)	Age, height, smoking, social class at birth
Strachan (1994)	Prospective cohort	1186	England & Wales	34-35	Obtained at birth	Positive linear trend of FEV_1 across quarters of birth weight ($p = 0.011$)	Not available	Sex, height, smoking, father's social class
Frankel (1996)	Prospective cohort	1258	Wales	45-59	Self-report	Positive linear trend of FEV_1 across quarters ($p=0.06$)	0.047 (0.023)	Age, height squared (male only study)
Stein (1997)	Birth cohort follow-up	286	India	38-59	Obstetric records	Change per 1lb birth weight: FEV_1 in men: 0.16 (-0.02, 0.33) l FEV_1 in women: 0.14 (0.00, 0.30) l	0.06 (0.03)	Age, height, body mass index, social class, smoking (results stratified by sex)
Shaheen (1998)	Retrospective cohort	239	Scotland	Mean (SD) 57.6 (4.3)	Obstetric record	Change per kg birth weight: FEV_1: 0.036 (-0.074, 0.147) l FVC: 0.010 (-0.119, 0.139) l	0.036 (0.057)	Age, sex, height, smoking and type of spyrometer
Lopuhaa (2000)	Retrospective cohort	726	The Netherlands	50	Birth records	p-values for linear trends across 4 categories of birth weight: FEV_1: $p = 0.6$ FVC: $p = 0.6$ FEV_1/FVC: $p = 0.8$	0.03 (0.03)	Age, sex, height

Table 4: continued

Cheung (2001)	Prospective birth cohort	120	China	30	Birth records	p-values for linear trends across 7 categories of birth weight: FEV_1: $p = 0.36$ FVC: $p = 0.87$ FEV_1/FVC: $p = 0.30$	Not available	Age, sex, height
Boezen (2002)	Prospective cohort	590	The Netherlands	18-22	Obstetric records	Change per 100g <u>decrease</u> in birth weight FEV_1: -0.013 (SE:0.004)	0.13 (0.04)	Age, height, smoking, maternal smoking in pregnancy, sex, birth order, gestational age
Edwards (2003)	Record linkage cohort study	323	Scotland	45-50	Obstetric records	p-values for linear trends across 5 categories of birth weight: FEV_1 Men: $p = 0.04$ FEV_1 Women: $p = 0.01$ FVC Men: $p < 0.01$ FVC Women: $p < 0.01$	Not available	Age, height, weight, smoking, deprivation category, sex, parity, gestational age

Table 4: continued

Laerum (2004)	Retrospective cohort	1514	Denmark Estonia Iceland Norway Sweden	20-44	Birth or Obstetric records	Change per 500g birth weight FEV_1: 0.45 (-0.52, 1.41) % predicted FVC: 0.47 (-0.52, 1.46) % predicted	0.09 (0.024)	Age, gender, height, prematurity, study centre (country), BMI, allergic rhinitis, parental and adult smoking (the results in the published study were also adjusted for birth length; the results included in our meta-analysis were NOT adjusted for birth length)

* These were either calculated from the information provided or from information obtained from the authors; SE: Standard error

Legend and footnotes for figures

Figure 1: Meta-analysis of adult studies of the association between birth weight and forced expiratory volume in 1 second measured in adulthood

Footnote to figure 1: The figure shows the regression coefficient (the change in FEV_1 (L) per increase in 1kg birth weight) and 95% confidence intervals for each individual study. The boxes represent the regression coefficient and the size of the box indicates the weight given to that study in the meta-analysis (greater weight given to larger studies); the horizontal lines represent the 95% confidence intervals. The diamond is the pooled effect obtained from combining the coefficients of each study. The vertical points of the diamond indicate the pooled regression coefficient and the two horizontal points the lower and upper 95% confidence intervals.

Figure 1: Meta-analysis of adult studies of the association between birth weight and forced expiratory volume in 1 second measured in adulthood