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EARLY GROWTH AND ADULT RESPIRATORY FUNCTION IN MEN AND WOMEN FOLLOWED FROM THE FOETAL PERIOD TO ADULTHOOD

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ABSTRACT
Rationale: While some studies suggest that poor foetal growth rate, as indicated by lower birth weight, is associated with poor respiratory function in childhood, findings among adults remain inconsistent.
Objective: To determine the association between early growth and adult respiratory function
Methods: Longitudinal birth cohort study of 5390 men and women born full term and prospectively followed from the foetal period to adulthood
Measurements: Weight at birth and infancy, and forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) as assessed by standard spirometry at age 31 years.
Main results: Adult FEV_1 and FVC increased linearly with higher birth weight in both men and women with no apparent threshold. After adjustment for sex, adult height and other potential confounders operating through the lifecourse, every 500 g higher birth weight was associated with higher FEV_1 by 53.1 [95% confidence interval (CI) 38.4 to 67.7] ml and higher FVC by 52.5 (95% CI 35.5 to 69.4) ml. These positive associations persisted across categories of smoking, physical activity and body-mass index, with the lowest respiratory function noted among those with lower birth weight who were smokers, led sedentary lifestyle or were overweight. Weight gain in infancy was also positively associated with adult lung function.
Conclusion: Birth weight was continuously and independently associated with adult respiratory function. It is plausible that poor growth in early life may restrict normal lung growth and development, which could have long-term consequences on lung function later in life.

Key words: Birth weight; postnatal growth; respiratory function tests

INTRODUCTION

Children born with lower birth weight tend to have poorer lung function when compared with children with higher birth weight,[1-4] though longitudinal data assessing the relation between birth weight and adult lung function are limited and findings have been conflicting.[5-14] The apparent inconsistencies could be due to small sample sizes, biases associated with the retrospective collection of birth weight data, high proportion of persons lost to follow-up, or lack of information on potential confounders and mediating factors that may operate through the lifecourse.

As poor lung function in adulthood is consistently shown as an independent predictor of all-cause mortality and deaths due to respiratory and cardiovascular diseases,[15,16] identifying whether the influence of lower birth weight on impaired respiratory function extends to adulthood could have important clinical and public health implications. We examined the relation between birth weight, as a marker of general foetal growth, growth in infancy, and subsequent adult respiratory function assessed at age 31 years in a large population-based cohort of men and women prospectively followed from the foetal period to adulthood.

METHODS

Participants and data collection

Recruitment and data collection of the 1966 Northern Finland Birth Cohort (NFBC) have been described elsewhere.[17] Briefly, the original birth cohort consisted of offspring (n=12 058 livebirths with birth weight ≥600 g, and 94.5% born at ≥37 gestational weeks) of all pregnant women in Northern Finland with expected deliveries in 1966. Women were recruited and baseline data were collected by questionnaire during routine prenatal health check at maternity health centers, with about 80% visiting the centers for the first time by the 16th gestational week. The course of pregnancy and data on birth at the time of delivery (99% in hospitals) were prospectively recorded. Growth data of offspring were collected at approximately 1 year of age from child welfare centers, which have been established as part of the comprehensive welfare health system in Finland since 1944.[18] Data on hospital admissions were obtained from hospital records and from national hospital discharge register. Follow-up in 1997 to 1998 consisted of questionnaires sent to all cohort members, as well as clinical examination of those living in Northern Finland or in the capital city area.[19] The University of Oulu Ethics Committee approved the study and participants gave written informed consent.

Early life variables

Birth weight (to the nearest 10 grams) was measured immediately after birth. Gestational age at birth was computed as number of completed weeks from date of mother's last menstrual period to delivery. Weight was also measured around 12 months of age (mean=12.3, range 10th to 14th months); we calculated weight gain during first year by subtracting birth weight from this value. Mothers were classified as smokers if they smoked at least one cigarette per day during pregnancy, quitters if they smoked at any time during 12 months preceding but not during pregnancy, and non-smokers if they neither smoked from 12 months preceding nor during pregnancy. Prenatal social class was based on father's occupation (I – professionals, II – skilled workers, III – unskilled workers, and IV – farmers), or mother's occupation if missing. Using International Classification of Diseases - 8, we identified children admitted to hospitals with diagnoses of acute respiratory illness or pneumonia occurring up to age 7 years as at these ages respiratory infection has been associated with reduced adult respiratory function.[20] We also identified participants who had physician-diagnosed asthma at age 14 years assessed from questionnaires sent to participants and parents in 1980.

Adult variables

In 1997, 97% (n=11 637) of the cohort were alive, of whom 7.4% (n=856) were abroad and 0.8% (n=96) untraced. In 1997 to 1998, those living in Northern Finland or Helsinki area (n=8463) were invited to a clinical examination conducted by trained nurses using a standardised procedure. Respiratory function was assessed by forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) using a Vitalograph P-model spirometer (Vitalograph Ltd., Buckingham, UK), with a volumetric accuracy of ±2% or ±50 ml whichever was greater. The spirometer was calibrated regularly using a 1-Litre precision syringe. The spirometric manoeuvre was performed three times but was repeated if the difference between two maximal readings was >4%. We used the highest FEV_1 and FVC measurement. We also measured weight and height and calculated body-mass index (BMI) as weight/height^2, and defined overweight as BMI ≥25 kg/m^2. We classified participants as having a high level of physical activity if they were engaged in brisk physical activities (causing some sweating and breathlessness) at least 2-3 times a week for at least 20 minutes at a time [the approximate minimum level of activity which could enhance either fitness or health[21]]. Current smokers were defined as smoking cigarettes daily for at least a year, former smokers if they previously smoked cigarettes but stopped for at least one year previously, and never smokers if they had neither currently nor previously smoked cigarettes daily for at least a year. Adult social class was based on highest education attained at 31 years (I – university degree, II – secondary or polytechnic school, III – vocational school, and IV – others, including unknown or no education after elementary school). We also noted any history of physician-diagnosed asthma and emphysema or chronic bronchitis.

Statistical analysis

There were 6033 participants to the clinical examination at age 31 years. We excluded those with missing or inadequate spirometric findings (n=153), those born at <37 weeks (n=275) and women who were pregnant during clinical assessment (n=216). Our analyses included the remaining 5390 participants (2684 men, 2706 women).

We analysed results separately for men and women. We used multiple linear regression to estimate difference in respiratory function per 500 g higher birth weight (one SD of birth weight = 497 g) and per 1 kg higher weight gain during first year (available for 2262 men and 2295 women; one SD of weight gain during first year = 1.1 kg). Covariates included gestational age at birth, adult height and adult weight, history of acute respiratory infection or pneumonia in childhood, maternal smoking during pregnancy, parental social class at birth, and adult cigarette smoking, physical activity level and social class. As covariates, we used gestational age and adult height and weight as continuous variables in the regression models. We also mutually adjusted for birth weight and weight gain during first year. We calculated mean FEV_1 and FVC by tertile of birth weight stratified by tertile of weight gain during first year or by adult smoking, physical activity or BMI.

We calculated expected FEV_1 for men and women who were never smokers and without emphysema or chronic bronchitis using sex-specific regression with height as an explanatory variable and calculated percent predicted FEV_1 [(actual FEV_1/expected FEV_1) x 100]. We also calculated the ratio of FEV_1 to FVC. We assessed interactions of birth weight with weight gain during first year, adult smoking, adult physical activity or adult BMI by analysis of variance. We used BMI to define overweight and for assessing interaction with other covariables. In our analyses for FEV_1:FVC, the covariates used in the regression models were similar as those used in our separate analyses for FEV_1 and FVC. However, we only adjusted for gestational age, maternal smoking during pregnancy, adult weight, and adult physical activity in the multivariate regression models for predicted FEV_1. We used two-sided p values and considered any result with $p<0.05$ as statistically significant. We analysed our data using STATA 8 (College Station, Texas, USA) statistical software.

RESULTS

Baseline characteristics of study participants

Compared to the remaining cohort members born full term, the 5390 study participants had 80 g higher birth weight and 0.4 weeks longer gestational age at birth (both $p<0.001$) but did not significantly differ in weight gained during their first year ($p>0.05$). Characteristics of study participants are described in table 1 (see table S1, online supplement, for characteristics by birth weight quintile). Mean (SD) birth weight was 3592 (512) g in men and 3467 (474) g in women; mean (SD) weight gain during first year was 7.0 (1.1) kg in men and 6.5 (1.1) kg in women. Respective means (SD) for FEV_1 in men and women were 4.54 (0.62) and 3.41 (0.47) L, and for FVC were 5.48 (0.75) and 4.02 (0.55) L.

Table 1. Characteristics of men and women in the 1966 Northern Finland Birth Cohort study.

Characteristics	Men	Women
Number	2684	2706
Early life factors		
Birth weight, grams	3592 ±512	3467 ±474
Weight gain during first year*, kilograms	7.0 ±1.1	6.5 ±1.1
Gestational age at birth, weeks	40.2 ±1.5	40.3 ±1.5
% Parental social class III and IV at birth† (n)	47.5 (222)	40.9 (220)
% Mothers smoking during pregnancy (n)	13.3 (349)	12.3 (324)
% Childhood respiratory infection‡ (n)	6.7 (181)	5.0 (135)
Factors at age 31 years		
Forced expiratory volume in 1 second (FEV_1), liters	4.54 ±0.62	3.41 ±0.47
Forced vital capacity (FVC), liters	5.48 ±0.75	4.02 ±0.55
FEV_1:FVC ratio, percent	83.1 ±6.4	85.0 ±6.5
Predicted forced expiratory volume in 1 second, percent	99.2 ±11.7	101.8 ±11.7
Height, meters	1.78 ±0.8	1.65 ±0.6
Weight, kilograms	80.2 ±12.7	65.6 ±12.5
Body-mass index, kilograms/meter^2	25.2 ±3.6	24.2 ±4.7
% Current cigarette smokers (n)	32.7 (878)	23.0 (622)
% Known asthma at 14 or 31 years§ (n)	8.3 (223)	10.5 (284)
% Known emphysema or chronic bronchitis§ (n)	5.4 (144)	5.9 (160)
% Low physical activity level‖ (n)	42.9 (1151)	41.7 (1129)
% Social class III and IV** (n)	66.0 (308)	50.7 (249)

Data presented as mean ± standard deviation for all continuous variables; *Measured between the 10th to 14th month and data available for 2262 men and 2295 women; †Parental social class (III – unskilled/others, IV – farmers); ‡Hospital diagnosis of acute respiratory infection or pneumonia between 0 to 7 years; §Physician-diagnosis; ‖Participation in brisk activity of at least 20 minutes was less than twice a week; **Adult social class (III – vocational, IV – no education beyond elementary school/unknown).

Birth weight, weight gain at 1 year and respiratory function at age 31 years
Respiratory function (FEV_1, FVC and % predicted FEV_1) linearly increased across the whole range of birth weight quintile (p for trend<0.001) without any apparent threshold. Mean differences in respiratory function between top and bottom birth weight quintiles in men were 368 ml (FEV_1) and 459 ml (FVC), and in women were 290 ml (FEV_1) and 314 ml (FVC) (Table S1, online supplement). These mean differences (95% CI) reduced to 169 (95 to 242) ml for FEV_1 and 180 (95 to 266) ml for FVC in men, and 141 (84 to 198) ml for FEV_1 and 115 (49 to 180) ml for FVC in women after adjusting for gestational age, maternal smoking during pregnancy and adult factors (height, cigarette smoking, weight and physical activity). Mean FEV_1:FVC ratio did not vary significantly across birth weight quintile (p for trend in men=0.56 and in women=0.31) (Table S1, online supplement). After adjusting for aforementioned covariates, a significant increasing trend across birth weight quintiles were observed only among women (p=0.047). The magnitude difference in the adjusted mean FEV_1:FVC ratio (95% CI) between the top and lowest birth weight quintile in men was 0.4 (-0.5 to 1.3) % and in women was 1.1 (0.2 to 2.0) %. Adjusting for gestational age, maternal smoking during pregnancy and adult weight and physical activity, the difference in mean predicted FEV_1 (95% CI) between the top and lowest birth weight quintile in men was 3.7 (2.1 to 5.2) % and 4.4 (2.8 to 6.0) %.

Both FEV_1 and FVC were significantly higher for every 500 g higher birth weight (table 2), though the size of the coefficients was reduced by about half with adjustment for gestational age and adult height. The estimates remained significant with further adjustment for various potential confounders across the lifecourse – even among relatively healthy men and women. Combining data for men and women and adjusting for sex, gestational age, maternal smoking during pregnancy and other adult factors, every 500 g higher birth weight was associated with higher FEV_1 by 53.1 (95% 38.4 to 67.7) ml and higher FVC by 52.5 (95% CI 35.5 to 69.4) ml. A significant association between birth weight and FEV_1:FVC ratio was observed in women (but not in men) after adjusting for covariates. The estimated difference in predicted FEV_1 for every 500 g higher birth weight was 1.3 (95% CI 0.8 to 1.8) % in men and 1.5 (95% CI 1.0 to 2.0) % in women after adjusting for gestational age at birth and adult factors (height, cigarette smoking, weight and physical activity). Adding a quadratic term for gestational age in the multivariate models used in Table 2 did not materially alter the results.

Table 2. Estimated difference in respiratory function, assessed at age 31 years, for every 500 g higher birth weight in 5390 men and women in the 1966 Northern Finland Birth Cohort study.

Covariates adjusted for in regression models:	**FEV_1 (ml)**	**FVC (ml)**	**FEV_1:FVC ratio (%)**
	β (95% CI)	β (95% CI)	β (95% CI)
MEN (N= 2684)			
Unadjusted	127.7 (105.4 to 150.1)	160.4 (133.4 to 187.5)	-0.11 (-0.35 to 0.12)
Height† at 31 years	47.0 (26.6 to 67.4)	49.6 (26.0 to 73.2)	0.09 (-0.16 to 0.33)
Gestational age* and height† at 31 years	57.4 (35.1 to 79.7)	59.4 (33.5 to 85.2)	0.13 (-0.14 to 0.39)
Gestational age,* maternal smoking during pregnancy and height† at 31 years	54.6 (32.1 to 77.2)	57.8 (31.6 to 84.0)	0.10 (-0.17 to 0.37)
Gestational age,* maternal smoking during pregnancy and adult factors†‡	57.8 (35.1 to 80.4)	61.6 (35.3 to 88.0)	0.11 (-0.16 to 0.38)
Lifecourse factors‖	57.5 (34.9 to 80.1)	61.4 (35.1 to 87.7)	0.11 (-0.16 to 0.38)
Subgroup of men†§ (N=1893)	56.3 (30.4 to 82.3)	56.6 (25.7 to 87.5)	0.16 (-0.14 to 0.45)
WOMEN (N=2706)			
Unadjusted	105.8 (87.7 to 123.9)	119.9 (98.3 to 141.4)	0.12 (-0.14 to 0.38)
Adjusted for height† at 31 years	39.6 (23.2 to 56.1)	33.6 (14.5 to 52.6)	0.27 (0.07 to 0.54)
Adjusted for gestational age* and height† at 31 years	45.5 (27.8 to 63.2)	41.0 (20.7 to 61.3)	0.26 (-0.03 to 0.54)
Gestational age,* maternal smoking during pregnancy and height† at 31 years	44.8 (26.8 to 62.9)	41.9 (21.2 to 62.6)	0.22 (-0.07 to 0.51)
Gestational age,* maternal smoking during pregnancy and adult factors†‡	48.2 (30.0 to 66.4)	42.3 (21.3 to 63.2)	0.30 (0.01 to 0.60)
Lifecourse factors‖	48.8 (30.3 to 66.6)	42.3 (21.3 to 63.2)	0.31 (0.01 to 0.60)
Subgroup of women†§ (N=1880)	52.7 (31.2 to 74.3)	43.7 (19.1 to 68.2)	0.41 (0.04 to 0.77)

FEV_1 denotes forced expiratory volume in 1 second, FVC denotes forced vital capacity, CI denotes confidence interval, OR denotes odds ratio, s denotes second; *At birth; †Excludes height as covariate for regression models for predicted FEV_1; ‡Adult facotrs: height, weight, cigarette smoking (never, former and current), and physical activity level (high versus low) at 31 years; ‖Gestational age at birth, maternal smoking during pregnancy, aforementioned adult factors as well as hospital diagnosis of respiratory infection between 0 to 7 years, other respiratory illnesses (physician diagnoses of asthma at age 14 or 31 years or emphysema/chronic bronchitis at 31 years), social class at birth (I, II, III and IV) and at age 31 years (I, II, III and IV); §Excludes those with hospital diagnosis of respiratory infection between 0 to 7 years, whose mothers smoked during pregnancy and had physician-diagnoses of asthma (at 14 or 31 years) or emphysema/chronic bronchitis at 31 years, and adjusted for gestational age at birth, aforementioned factors at 31 years and social class at birth (I, II, III and IV) and at age 31 years (I, II, III and IV).

Weight gain during first year was positively associated with lung function in men and women, with the regression coefficients increasing in magnitude when models were further adjusted for birth weight (table 3), although the confidence limits crossed the null association for FEV_1 in men. Those in the lowest birth weight category who gained more weight in infancy tended to have higher FEV_1 than those who gained less weight (figure 1; see figure S1, online supplement, for FVC results), although statistically significant interaction between birth weight and weight gain during first year was only observed for FEV_1 in women (p=0.046). Women in the top birth weight tertile with higher weight gain during the first year tended to have lower lung function values.

Statistical interaction was observed between birth weight and sex for FVC (p=0.007) but not for FEV_1 (p=0.11) or FEV_1:FVC ratio (p=0.16). Similarly, a statistical interaction was observed between weight gain at 1 year and sex for FVC (p=0.001), weakly for FEV_1 (p=0.067) but not for FEV_1:FVC ratio (p=0.17).

Table 3. Adjusted* regression of respiratory function, assessed at age 31 years, with birth weight and weight gain† during first year in men and women in the 1966 Northern Finland Birth Cohort study.

Regression models	**Men** (N= 2262)		**Women** (N=2295)	
MEN (N= 2262)	**FEV_1 (ml)** β (95% CI)	**FVC (ml)** β (95% CI)	**FEV_1 (ml)** β (95% CI)	**FVC (ml)** β (95% CI)
Model 1: Birth weight (per 500g)	60.5 (35.1 to 85.9)	64.4 (35.2 to 93.6)	54.1 (34.4 to 73.8)	47.3 (24.8 to 70.0)
Model 2: Weight gain during first year† (per 1 kg)	12.3 (-10.1 to 34.6)	41.8 (16.1 to 67.4)	12.0 (-4.3 to 28.4)	23.5 (4.9 to 42.0)
Model 3: Birth weight (per 500g)	63.7 (38.1 to 89.3)	72.4 (43.0 to 101.8)	57.5 (37.6 to 77.4)	52.6 (29.9 to 75.3)
Weight gain during first year† (per 1 kg)	20.1 (-2.4 to 42.5)	50.6 (24.8 to 76.4)	19.0 (2.6 to 35.4)	29.8 (11.1 to 48.5)

Analysis restricted to participants with data on weight gain during first year; FEV_1 denotes forced expiratory volume in one second, FVC denotes forced vital capacity and CI denotes confidence interval; *Adjusted for gestational age at birth, maternal smoking during pregnancy as well as factors at 31 years: adult height, weight, cigarette smoking (never, former and current) and physical activity level (high versus low); †Weight during first year minus birth weight; ‡Birth weight and weight gain during first year included as explanatory variables either separately (models 1 and 2) or together (model 3) in the regression model.

Birth weight, adult characteristics and respiratory function at age 31 years

Higher FEV_1 was noted with higher birth weight tertile across all categories of cigarette smoking, physical activity and BMI categories at age 31 years (figure 2; see figure S2, online supplement, for FVC results). Lowest values were observed among those in the bottom birth weight tertile and were smokers, had low physical activity level, or were overweight. Participants with favourable profiles on these lifestyle variables but were at the lowest birth weight tertile had comparable, or even lower, FEV_1 than those at the top birth weight tertile who were smokers, had lower physical activity level or were overweight. We did not observe any significant interaction between birth weight and these adult variables ($p>0.05$) except in smoking for FEV_1 ($p=0.03$ in men). The interactions between adult smoking and adult BMI for FEV_1 and FVC in both men and women were not significant (all $p>0.05$).

DISCUSSION

Respiratory function, assessed by FEV_1 and FVC at age 31 years, increased linearly across the whole range of birth weight in both men and women with no apparent threshold. Weight gain during first year was positively associated with adult lung function independently of birth weight. These observations suggest that respiratory health in adulthood could be influenced by growth early in life.

The association between early life measures such as weight at birth and infancy and respiratory function measured 31 years later could simply reflect the effect of height, an important determinant of respiratory function,[22] as lower birth weight babies tend to be shorter in stature later in life[23] but present results were independent of adult height. The associations were independent of gestational age at birth, maternal smoking during pregnancy and childhood respiratory infections as well as by known asthma, or emphysema or chronic bronchitis in adulthood. The findings remained significant even after taking into account adult smoking habit, physical activity level and weight as well as social class at birth and in adulthood. Indeed, the magnitude of reduction in lung function was greatest among those who had lower birth weight and were current smokers, led sedentary lifestyle or had excess weight. Although spirometry assessment can be influenced by voluntary effort, it seems unlikely that there would be systematic differences in spirometry performance with respect to early life growth.

Earlier studies evaluating the association between birth weight and respiratory function have focused on highly selected participants or assessed outcomes in childhood,[1-4] when lung function has not reached the maximum potential. Few studies assessed the relation between birth weight and lung function in adulthood, and results were inconsistent. Some studies have shown no association between birth weight and adult lung function,[7,9,12-14] while others have found a positive relationship either with both FEV_1 and FVC[5,6,10,11] or with FEV_1 only but not FVC.[5] Consistent with other studies,[5,6,8] we found no trend in FEV_1:FVC ratio across quintiles of birth weight, although we found a weak but significant association among women. This sex-related difference in the findings was due to the weaker association of birth weight with FVC than with FEV_1 in women whereas the associations of birth weight with both measures were of similar magnitude in men.

Previous studies are limited by small sample sizes[6,7,9-11,13] use of self-reported birth weight,[14] retrospectively obtained perinatal information or reliance on the availability of birth weight data from historical records.[5-8,11,12] Other limitations include loss to follow-up of participants,[8,11] use of hospital-based populations,[9,10] and limited data for women[5] or men.[14] Our study was based on a large population-based cohort of men and women who were prospectively followed-up from the foetal period to adulthood. Further, our birth weight data were obtained immediately after birth, minimising errors associated with timing, inaccurate recall and rounding off of birth weight measurement.

These limitations could have important implications in determining the strength of the association between early growth and adult lung function. A meta-analysis of these studies suggested that 1 kg of birth weight was associated with an increase in FEV_1 by 48 (95% CI 26 to 70) ml after adjusting for age, smoking and height.[14] Using a similar regression model, per 1 kg change in birth weight in our cohort was associated with a difference in FEV_1 by 96.1 (95% CI 55 to 137.2) ml in men and 80.0 (95% CI 47.0 to 113.2) ml in women [combined estimates for men and women after further adjustment for sex was 89.2 (95% CI 62.6 to 115.8) ml]. Taking into account other factors through the lifecourse suggest that these estimates might be slightly higher (table 2). The estimate in the meta-analysis may reflect non-random measurement errors which could have weakened the true association. Our findings suggest that the association between birth weight and adult lung function could be stronger than previously shown.

Less studied is the impact of postnatal growth on adult lung function. It has been suggested that lower birth weight babies with higher postnatal weight gain may develop metabolic abnormalities and cardiovascular disease in adulthood.[24] One study suggested that small babies who gained greater weight at 5-14 weeks had diminished infant lung function compared to those who gained less weight.[25] In our cohort, postnatal weight gain among those in the lowest birth weight category was not associated with diminished adult lung function. Further, anthropometric measures at birth and at 12 months among Chileans were unrelated to FEV_1 which was measured in their late teens.[26] Actual data has not been presented in this paper but we speculate that age-related decline might heighten differences in lung function across birth weight gradient. Alternatively, ethnicity might also play a role. In a non-Caucasian population, birth weight was reported to be unrelated to adult lung function.[9]

Pulmonary development runs in parallel with the stage of bodily development at birth.[27,28] In humans, lung development continues postnatally with airway and alveolar formation and enlargement mainly continuing up to two years of age.[28,29] As foetal life is a period of rapid growth, any stimulus or insult at this critical period of early life development could permanently alter or ‘program’ structure and physiology of the respiratory system with possible long-term consequences.[30] Lower birth weight could indicate the effect of an adverse intrauterine environment which retards growth in utero and consequently constrains growth of airways and peripheral lung development. Since alveolar development continues into early infancy, impaired postnatal growth could also restrict further lung growth and differentiation.

The mechanism linking foetal growth retardation and impaired lung development is unclear. Maternal smoking during pregnancy is associated with lower birth weight,[31] impaired lung function in infancy[32] and childhood,[33] and higher lung function decline in young adulthood.[34] Although our findings were independent of maternal smoking during pregnancy, other factors such as maternal nutrition during pregnancy could play a role.[29] In animals, impairment in airway development has accompanied intrauterine growth restriction due to undernutrition.[35,36] Intrauterine growth restriction, which could also be due to excess foetal exposure to exogenous adrenocortical hormones,[37] is associated with elevated foetal cortisol level.[38] Prolonged early life exposure to glucocorticoids could have adverse affects on lung morphometry and alveolarisation.[39] Foetal growth retardation in itself may restrict lung distension, an important physical factor known to stimulate foetal lung growth.[40] Lower birth weight has been associated with lower proportion of lean mass[41] and lower muscular strength,[42] possibly affecting the muscular component of ventilation. As low birth weight has been associated with diminished lung function in infancy[4] and in childhood,[1-3] and pulmonary function has been shown to track in childhood and adolescence to adulthood,[43] it is plausible that the reduced adult lung function in lower birth weight babies reflect their failure to achieve maximum adult ventilatory capacity. Although our cohort is still mainly young to develop important clinical outcomes such as chronic obstructive pulmonary disease, diminished lung function in young adulthood could render them at higher risk of developing chronic obstructive airway disease later in life.[5]

Certain limitations have to be considered. We did not assess lung function serially over time, although a single measurement of pulmonary function in adulthood has consistently shown to predict important health outcomes in different populations.[15,16] Further, the relatively increased age-related pulmonary function decline is normally observed in the late thirties therefore our estimates are probably more stable and less affected by these rapid changes.[44] However, we may not be able to assess changes over time separately for FEV_1 and FVC which might have implications in interpreting the age-related or sex-specific decline in FEV_1:FVC ratio.[44] Reversibility of airflow limitation was not examined but we previously showed that birth weight was unrelated to asthma or skin atopy.[45] We also could not rule out common underlying genetic explanation for foetal growth retardation and reduced adult lung function. On the other hand, an important strength is that we were able to include prospectively collected data on potential confounders and mediating factors operating throughout the lifecourse.

Babies with lower birth weight and poor infant growth may be at a higher risk for developing impaired adult pulmonary function. Our findings suggest that impaired respiratory function may be preventable or modifiable through the lifecourse – from targeting better maternal health during pregnancy, improved nutrition in infancy, and adopting healthy lifestyle in adulthood.

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COMPETING OF INTEREST

None declared

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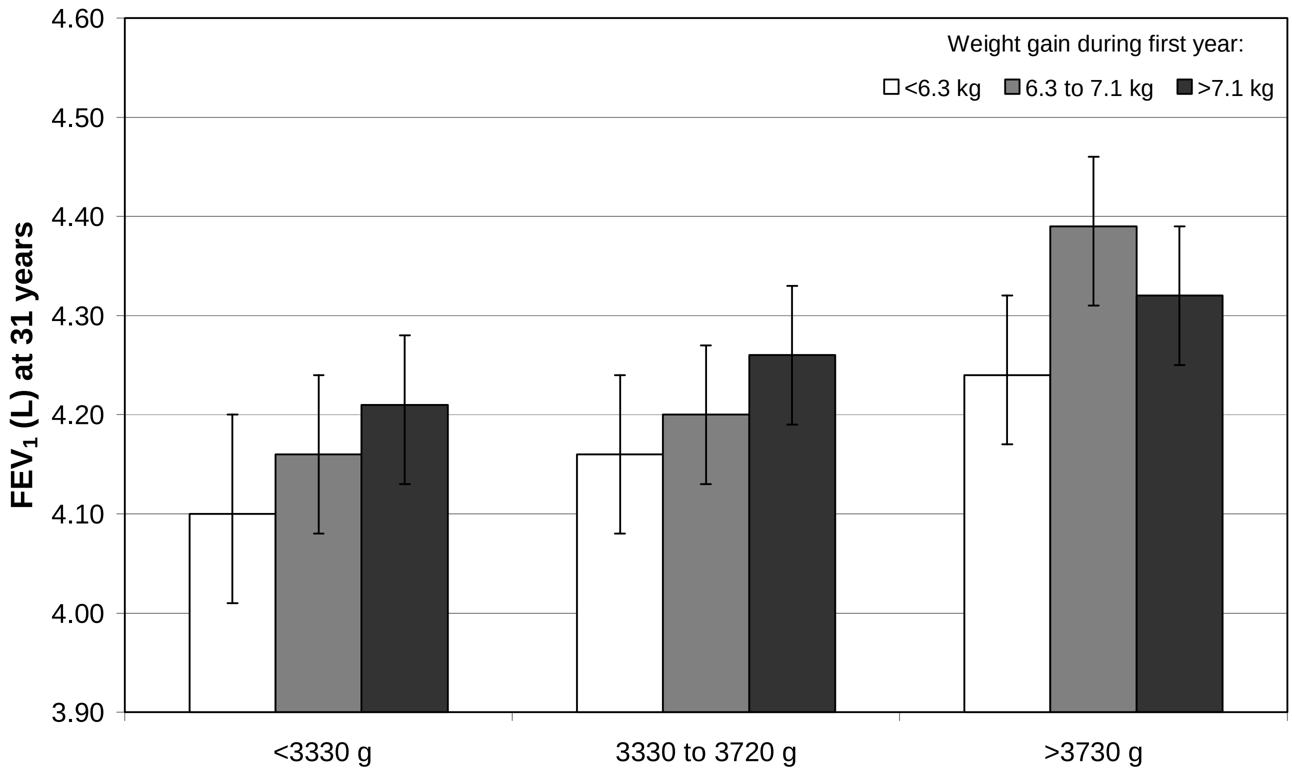
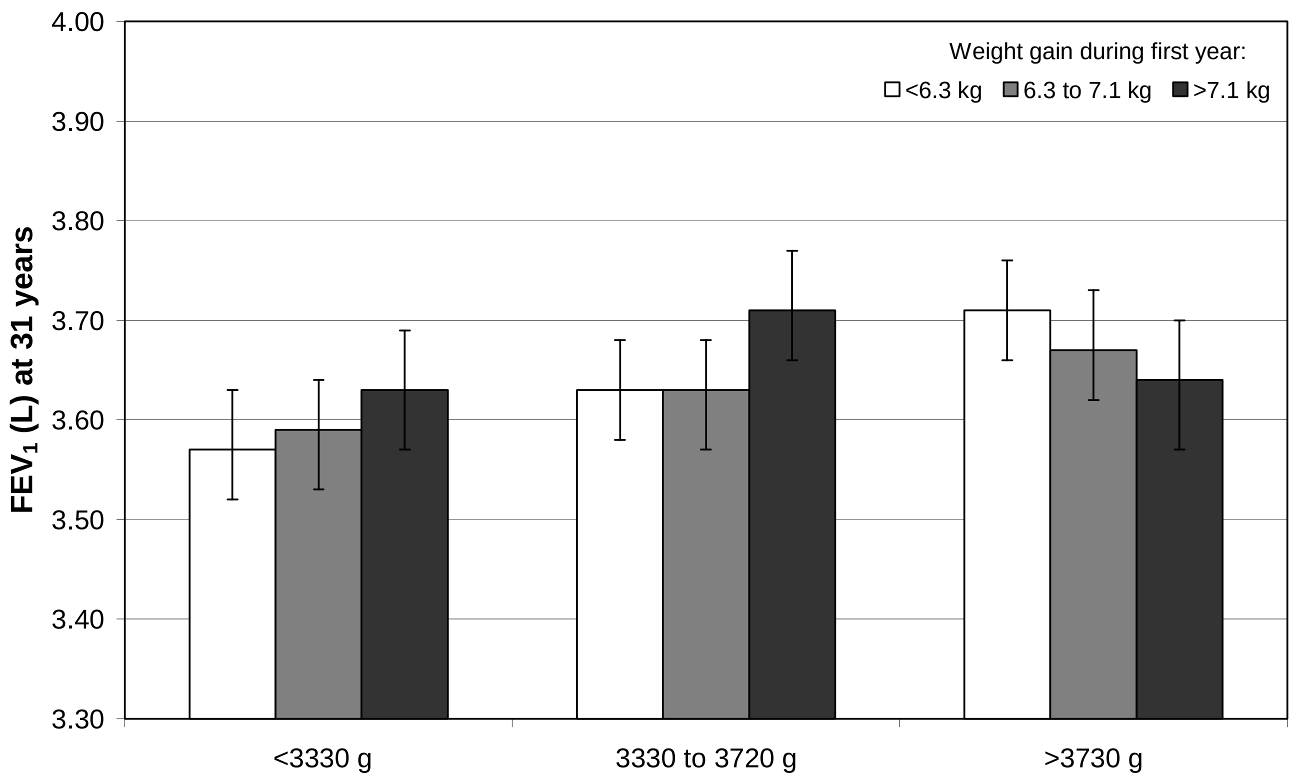
Figure 1. Forced expiratory volume in 1 second (L) at age 31 years by tertiles of birth weight and weight gain during first year in men and women in the 1966 Northern Finland Birth Cohort study. Figure shows mean values and 95% confidence limits for men (A) and women (B). FEV_1 denotes forced expiratory volume in 1 second; Values obtained from regression models and adjusted for gestational age at birth, maternal smoking during pregnancy, and factors at 31 years: height, weight, cigarette smoking (never, former and current), and physical activity level (high versus low); P for interaction between birth weight and weight gain during first year was 0.88 in men and 0.04 in women.

Figure 2. Forced expiratory volume in 1 second (L) at age 31 years by tertile of birth weight stratified by adult characteristics of men and women in the 1966 Northern Finland Birth Cohort study. Figure shows mean values and 95% confidence limits for men (A) and women (B); FEV_1 denotes forced expiratory volume in 1 second; Values obtained from regression models and adjusted for gestational age at birth, maternal smoking during pregnancy and factors at 31 years: height, weight, cigarette smoking (never, former and current), and physical activity level (high versus low) except for factor under consideration or weight for analysis using body-mass index (weight/height^2); Smokers were current smokers, and non-smokers were never and former smokers combined; High physical activity level defined as participation in brisk activity of at least 20 minutes twice a week and low level if participation is less in duration and/or frequency per week; P for interactions: birth weight and smoking (men=0.03, women=0.31), birth weight and physical activity (men=0.09, women=0.41), and birth weight and body-mass index (men=0.54, women=0.30).

Figure 1

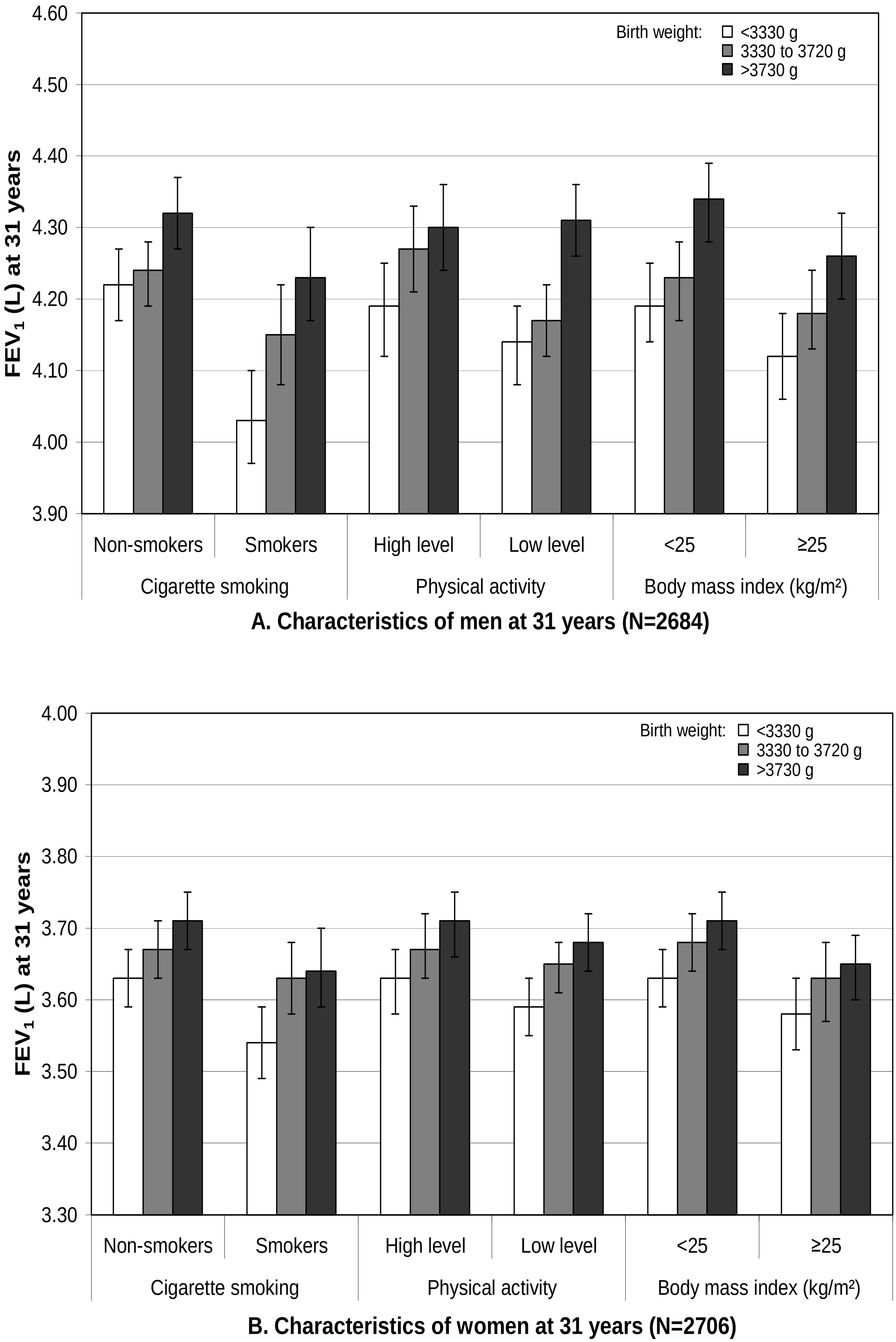


A. Birth weight in men (N=2346)



B. Birth weight in women (N=2385)

Figure 2



Birth weight:
<3330 g
3330 to 3720 g
>3730 g
FEV₁ (L) at 31 years
4.60
4.50
4.40
4.30
4.20
4.10
4.00
3.90
Non-smokers
Smokers
High level
Low level
<25
≥25
Cigarette smoking
Physical activity
Body mass index (kg/m²)
A. Characteristics of men at 31 years (N=2684)
Birth weight:
<3330 g
3330 to 3720 g
>3730 g
FEV₁ (L) at 31 years
4.00
3.90
3.80
3.70
3.60
3.50
3.40
3.30
Non-smokers
Smokers
High level
Low level
<25
≥25
Cigarette smoking
Physical activity
Body mass index (kg/m²)
B. Characteristics of women at 31 years (N=2706)

EARLY GROWTH AND ADULT RESPIRATORY FUNCTION IN MEN AND WOMEN FOLLOWED FROM THE FOETAL PERIOD TO ADULTHOOD

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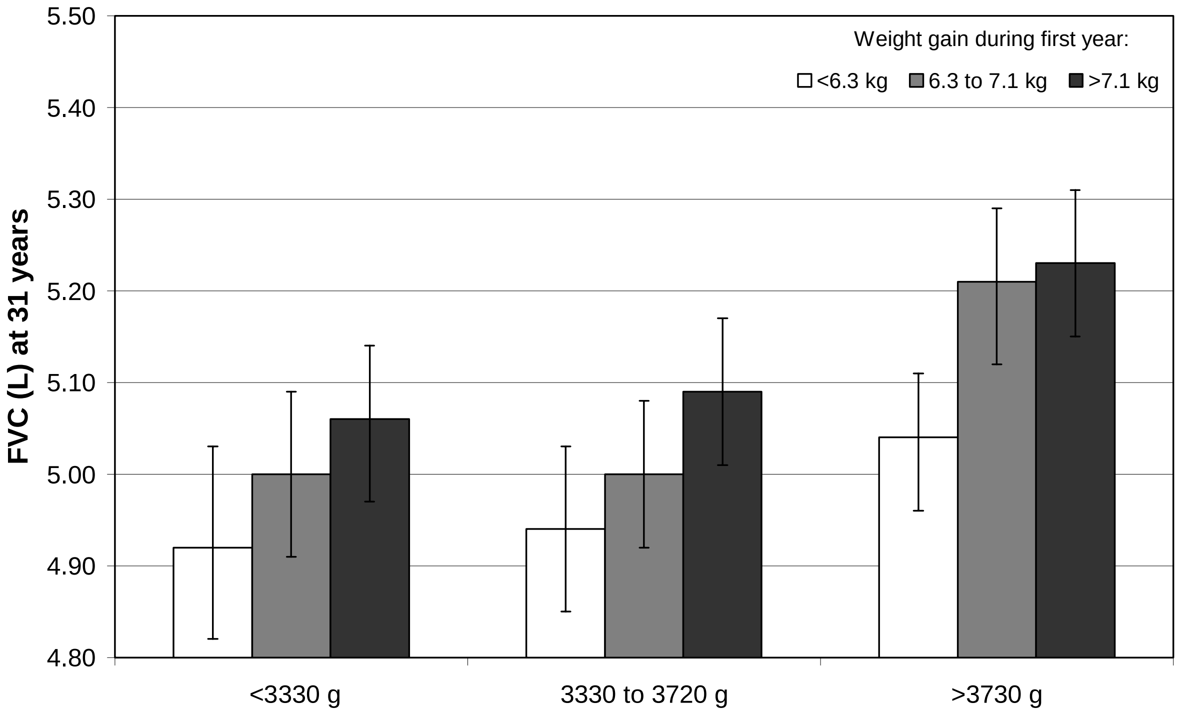
Online Data Supplement

Table S1. Characteristics of men and women in the 1966 Northern Finland Birth Cohort study by quintile of birth weight.

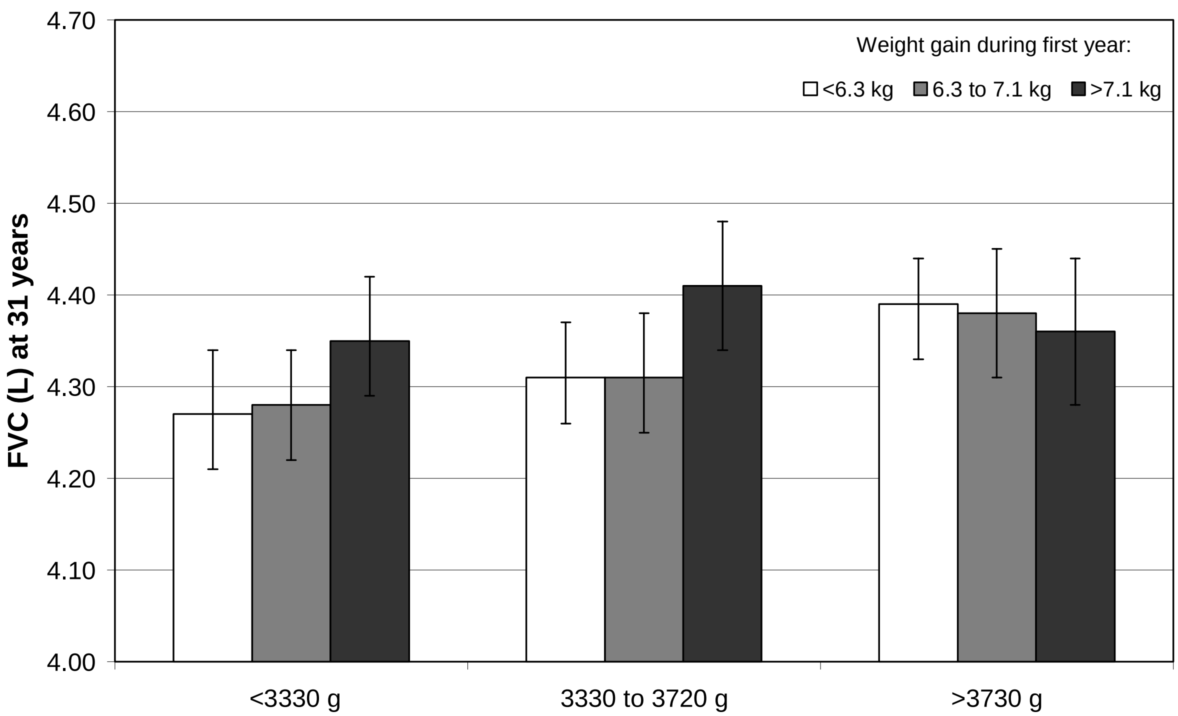
Variables	Birth weight quintile (g)				
	<3130	3130 to 3400	3410 to 3640	3650 to 3920	≥3920
MEN (Number)	467	501	491	565	660
Birth weight, g	2846 ±249	3282 ±84	3527 ±63	3775 ±82	4246 ±284
Weight gain during first year*, kg	7.2 ±1.1	7.0 ±1.0	6.9 ±1.1	7.0 ±1.0	6.9 ±1.2
Gestational age at birth, weeks	39.3 ±1.4	40.1 ±1.4	40.2 ±1.4	40.6 ±1.5	40.8 ±1.3
Height at 31 y, m	1.76 ±0.06	1.77 ±0.06	1.78 ±0.06	1.79 ±0.06	1.81 ±0.06
Weight, kg	77.2 (12.7)	78.7 (11.8)	79.8 (12.4)	81.0 (12.8)	83.2 (12.7)
Body-mass index† at 31 y, kg/m^2	24.9 ±3.7	25.1 ±3.5	25.3 ±3.6	25.3 ±3.8	25.5 ±3.5
Forced expiratory volume in 1 s at 31 y, L	4.37 ±0.59	4.46 ±0.61	4.49 ±0.61	4.59 ±0.61	4.74 ±0.61
Forced vital capacity at 31 y, L	5.27 ±0.72	5.38 ±0.74	5.42 ±0.75	5.53 ±0.72	5.73 ±0.74
FEV_1:FVC‡ at 31 y	0.831 ±0.061	0.833 ±0.072	0.832 ±0.065	0.832 ±0.060	0.829 ±0.061
Predicted FEV_1 at 31 y, %	97.7 (11.4)	98.8 (11.9)	98.6 (11.5)	99.3 (11.7)	100.8 (11.2)
% Cigarette smoking at 31 y (n)	34.0 (159)	35.7 (179)	30.8 (151)	32.6 (184)	31.1 (205)
% Low physical activity level§ at 31 y (n)	57.1 (267)	57.5 (288)	56.1 (275)	59.1 (334)	55.9 (369)
% Known asthma¶ at 14 or 31 y (n)	7.3 (34)	9.4 (47)	8.6 (42)	7.6 (43)	8.6 (57)
% Known obstructive disease‖ at 31 y (n)	5.4 (25)	7.0 (35)	4.3 (21)	5.8 (33)	4.5 (30)
% Childhood respiratory infection** (n)	6.9 (32)	6.4 (32)	7.1 (35)	6.4 (36)	7.0 (46)
% Mothers smoking during pregnancy (n)	15.4 (72)	13.6 (68)	14.7 (72)	11.9 (67)	10.6 (70)
% Social class III and IV at birth†† (n)	47.5 (222)	45.5 (228)	44.4 (218)	40.5 (229)	42.4 (280)
% Social class III and IV at 31 y‡‡ (n)	66.0 (308)	65.7 (329)	66.3 (326)	63.2 (357)	64.2 (424)
WOMEN (Number)	615	625	538	528	400
Birth weight, g	2857 ±253	3275 ±84	3539 ±63	3778 ±84	4213 ±275
Weight gain during first year*, kg	6.6 ±1.0	6.6 ±1.1	6.6 ±1.1	6.5 ±1.1	6.3 ±1.1
Gestational age at birth, weeks	39.7 ±1.6	40.2 ±1.5	40.5 ±1.3	40.6 ±1.3	41.0 ±1.4
Height at 31 y, m	1.62 ±0.06	1.64 ±0.06	1.65 ±0.06	1.66 ±0.06	1.67 ±0.07
Weight, kg	62.2 (11.8)	65.3 (13.7)	66.1 (12.9)	66.7 (13.5)	69.1 (15.0)
Body-mass index† at 31 y, kg/m^2	23.6 ±4.2	24.3 ±5.0	24.3 ±4.7	24.2 ±4.7	24.8 ±5.2
Forced expiratory volume in 1 s at 31 y, L	3.27 ±0.46	3.37 ±0.43	3.41 ±0.45	3.46 ±0.46	3.56 ±0.50
Forced vital capacity at 14 or 31 y, L	3.87 ±0.53	3.98 ±0.53	4.02 ±0.54	4.09 ±0.54	4.19 ±0.60
FEV_1:FVC‡ at 31 y	0.848 ±0.070	0.850 ±0.058	0.852 ±0.060	0.849 ±0.069	0.855 ±0.068
Predicted FEV_1 at 31 y, %	98.2 (12.0)	99.6 (11.0)	99.7 (11.2)	100.0 (11.8)	101.8 (12.3)
% Cigarette smoking at 31 y (n)	23.3 (143)	22.6 (141)	22.9 (118)	21.4 (113)	25.3 (101)
% Low physical activity level§ at 31 y (n)	59.0 (363)	54.2 (339)	59.9 (322)	59.8 (316)	59.3 (237)
% Known asthma¶ at 14 or 31 y (n)	9.9 (61)	11.7 (73)	11.3 (61)	9.1 (48)	10.3 (41)
% Known obstructive disease‖ at 31 y (n)	4.7 (29)	7.7 (48)	5.8 (31)	4.9 (26)	6.5 (26)
% Childhood respiratory infection** (n)	6.3 (39)	4.6 (29)	4.5 (24)	4.4 (23)	5.0 (20)
% Mothers smoking during pregnancy (n)	15.8 (97)	13.6 (85)	11.0 (59)	10.2 (54)	7.3 (29)
% Social class III and IV at birth†† (n)	50.4 (310)	44.0 (275)	40.9 (220)	44.3 (234)	47.0 (188)
% Social class III and IV at 31 y‡‡ (n)	66.6 (311)	62.1 (311)	50.7 (249)	41.6 (235)	30.3 (200)

Data presented as mean ± standard deviation for all continuous variables; S denotes second, y denotes years, FEV_1 denotes forced expiratory volume in one second and FVC denotes forced vital capacity; *Measured between the 10^{th} to 14^{th} month and data available only for 4557 participants; †Weight/height^2; ‡Ratio of forced expiratory volume in one second to forced vital capacity; §Participation in brisk activity of at least 20 minutes is less than twice a week; ¶Physician-diagnosis; ‖Physician-diagnosed emphysema or chronic bronchitis; **Hospital diagnosis of acute respiratory infection or pneumonia at 0 to 7 years; ††Parental social class (III – unskilled/others, IV – farmers); ‡‡Adult social class (III – vocational, IV – no education beyond elementary school/unknown).

Figure S1. Forced vital capacity (L) at age 31 years by tertiles of birth weight and weight gain during first year in men and women in the 1966 Northern Finland Birth Cohort study. Figure shows mean values and 95% confidence limits for men (A) and women (B); FVC denotes forced vital capacity; Values obtained from regression models and adjusted for gestational age at birth, maternal smoking during pregnancy, and adult height, weight, cigarette smoking (never, former and current), and physical activity level (high versus low); P for interaction between birth weight and weight gain during the first year were 0.57 in men and 0.14 in women.

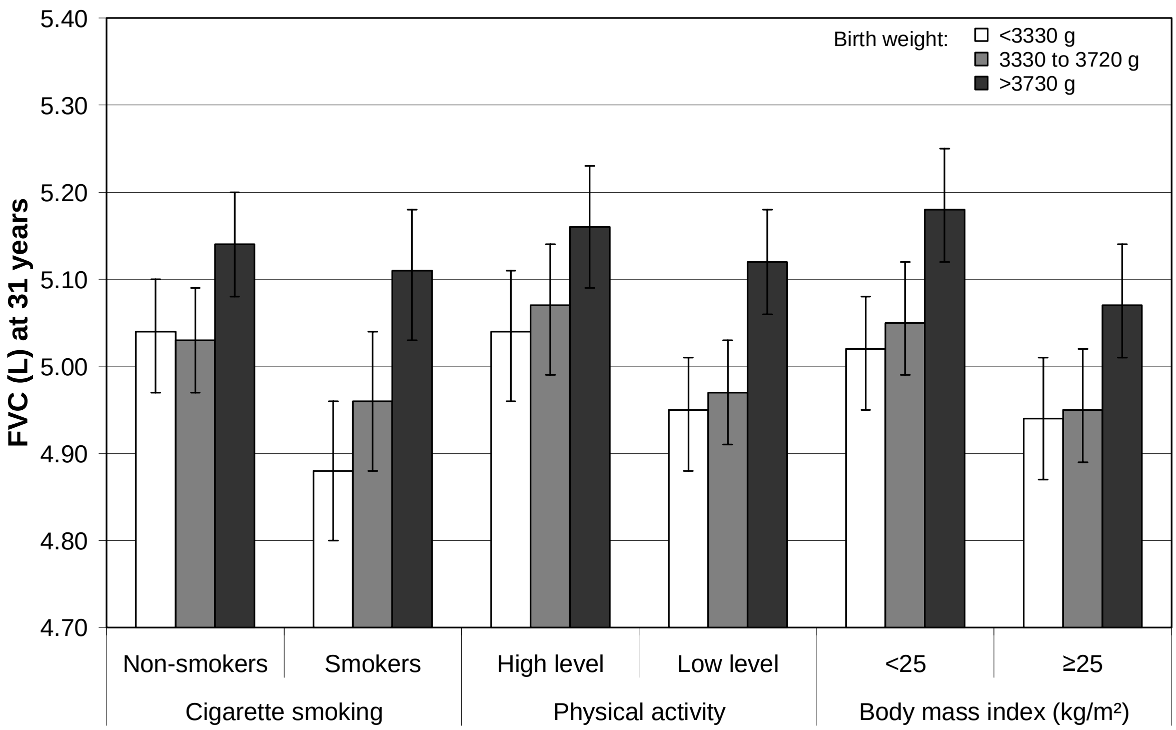


A. Birth weight in men (N=2346)

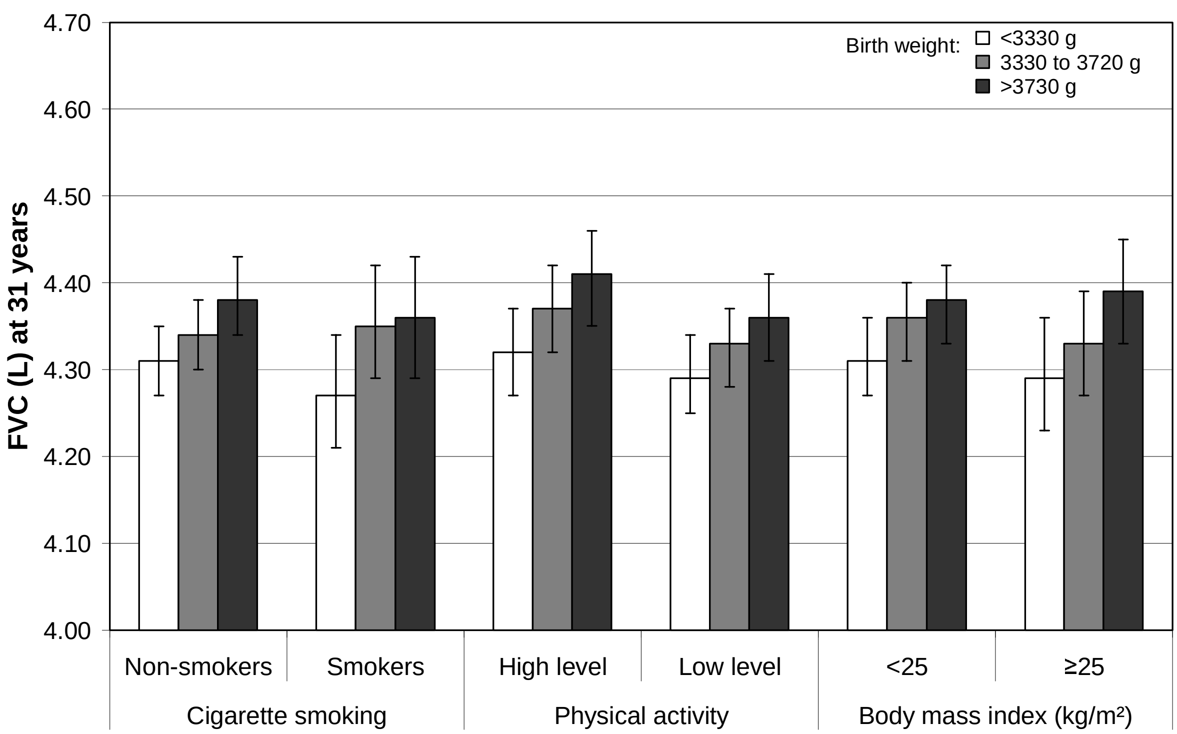


B. Birth weight in women (N=2385)

Figure S2. Forced vital capacity (L) at age 31 years by tertiles of birth weight stratified by adult characteristics of men and women in the 1966 Northern Finland Birth Cohort study. Figure shows mean values and 95% confidence limits for men (A) and women (B); FVC denotes forced vital capacity; Values obtained from regression models and adjusted for gestational age at birth, maternal smoking during pregnancy, and adult height, weight, cigarette smoking (never, former and current), and physical activity level (high versus low) except for factor under consideration or weight for analysis using body-mass index (weight/height^2); Smokers were current smokers, and non-smokers were never and former smokers combined; High physical activity level defined as participation in brisk activity of at least 20 minutes twice a week and low level if participation is less in duration and/or frequency per week; P for interactions: birth weight and smoking (men=0.11, women=0.70), birth weight and physical activity (men=0.29, women=0.47), and birth weight and body-mass index (men=0.69, women=0.62).



A. Characteristics of men at 31 years (N=2684)



B. Characteristics of women at 31 years (N=2706)