EDITOR'S
CHOICE

Early life origins of chronic obstructive pulmonary disease

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ABSTRACT

Background: Early life development may influence subsequent respiratory morbidity. The impact of factors determined in childhood on adult lung function, decline in lung function and chronic obstructive pulmonary disease (COPD) was investigated.

Methods: European Community Respiratory Health Survey participants aged 20–45 years randomly selected from general populations in 29 centres underwent spirometry in 1991–3 (n = 13 359) and 9 years later (n = 7738). Associations of early life factors with adult forced expiratory volume in 1 s (FEV_1), FEV_1 decline and COPD (FEV_1/FVC ratio <70% and FEV_1 <80% predicted) were analysed with generalised estimating equation models and random effects linear models.

Results: Maternal asthma, paternal asthma, childhood asthma, maternal smoking and childhood respiratory infections were significantly associated with lower FEV_1 and defined as "childhood disadvantage factors"; 40% had one or more childhood disadvantage factors which were associated with lower FEV_1 (men: adjusted difference 95 ml (95% CI 67 to 124); women: adjusted difference 60 ml (95% CI 40 to 80)). FEV_1 decreased with increasing number of childhood disadvantage factors (≥3 factors, men: 274 ml (95% CI 154 to 395), women: 208 ml (95% CI 124 to 292)). Childhood disadvantage was associated with a larger FEV_1 decline (1 factor: 2.0 ml (95% CI 0.4 to 3.6) per year; 2 factors: 3.8 ml (95% CI 1.0 to 6.6); ≥3 factors: 2.2 ml (95% CI −4.8 to 9.2)). COPD increased with increasing childhood disadvantage (1 factor, men: OR 1.7 (95% CI 1.1 to 2.6), women: OR 1.6 (95% CI 1.01 to 2.6); ≥3 factors, men: OR 6.3 (95% CI 2.4 to 17), women: OR 7.2 (95% CI 2.8 to 19)). These findings were consistent between centres and when subjects with asthma were excluded.

Conclusions: People with early life disadvantage have permanently lower lung function, no catch-up with age but a slightly larger decline in lung function and a substantially increased COPD risk. The impact of childhood disadvantage was as large as that of heavy smoking. Increased focus on the early life environment may contribute to the prevention of COPD.

Early life environment is most important for the development of asthma and atopy,[1–3] but there has been less focus on early life origins of chronic obstructive pulmonary disease (COPD).[1 4–6] The development of the bronchial tree is completed in terms of numbers of terminal bronchioles by the first trimester of pregnancy.[7] The final number of alveoli is established by the age of 2 years.[7 8] Thereafter, growth and functional development of the bronchial tree and the alveoli continue until a plateau phase is reached by the end of adolescence in women[9] and in the mid-20s in men.[10 11] It seems plausible that this period of development and growth of the lungs might be important for lung function and the development of COPD later in life.[5]

While smoking is a very important determinant for adult lung function and COPD, there is a wide variation in adult lung function that is not related to smoking[12] and that could possibly be explained by factors already determined early in life.[13] Maternal smoking is associated with lower lung function in infancy,[14–16] childhood[17] and adulthood.[18–20] An association between lower respiratory infections and adult lung function impairment is reasonably well documented.[5 6 21–23] Birth weight is consistently although weakly associated with lower adult lung function.[5 24 25] Childhood asthma is related to lower lung function in early adult life.[4 26–28]

This study examined the extent to which adult lung function and COPD are already determined in childhood compared with the impact of active smoking. We first identified early life environmental and genetic factors consistently associated with lower adult lung function; these were denoted "childhood disadvantage factors". We then investigated associations of childhood disadvantage with the level of adult lung function, lung function decline and COPD, and compared the impact of these with the impact of smoking. The analyses were performed using the European Community Respiratory Health Survey (ECRHS), a multicultural population from centres with wide variations in prevalence of COPD,[12] and included standardised spirometry measurements and extensive interview data for over 13 000 adults aged 20–56 years.

METHODS

Study subjects

The ECRHS II is the follow-up study of participants in ECRHS I, which selected adults aged 20–44 years from the general population in 1991–3. A total of 13 359 subjects (6624 men and 6735 women; 85% of those eligible) were included from random samples from 29 centres with lung function at ECRHS I. Of these, 7738 (57.9%) in 28 centres had lung function measured at ECRHS II in 1998–2002.[29] The mean follow-up time was 8.9 years (interquartile range 8.3–9.5) and the age range at follow-up was 26–56 years. The full protocol can be found at www.ecrhs.org.

Design

The investigation of lung function level and COPD was cross-sectional using data from both ECRHS I and II. Subjects only participating in ECRHS I contributed with one measurement, subjects participating in both surveys contributed with two measurements.

Longitudinal analysis of lung function decline was performed for subjects with lung function data in both surveys.

Childhood disadvantage

Participants responded to face-to-face interviewer-administered questionnaires including questions on early life factors, asthma and respiratory symptoms, and smoking habits. All available information in ECRHS I concerning early life (parental asthma, parental atopy, childhood asthma, childhood respiratory infections, parental smoking, family size and birth order, day care attendance, pet keeping and season of birth) was used for analysis. The questions are presented at www.ecrhs.org. "Childhood asthma" was defined as ever asthma with onset at or before the age of 10 years. Factors associated with adult forced expiratory volume in 1 s (FEV_1) in both men and women at a significance level of $p \leqslant 0.01$ after adjusting for smoking, education, social class, height, age and centre were defined as "childhood disadvantage factors". These factors were counted to create the variable "number of childhood disadvantage factors".

Lung function measurements and definition of COPD

The maximum FEV_1 and maximum forced vital capacity (FVC) of up to five technically acceptable manoeuvres were determined, and whether FEV_1 and FVC each met the American Thoracic Society (ATS) criterion for reproducibility. Decline in FEV_1 was expressed per year of follow-up (ECRHS II value minus ECRHS I value; a negative value represents a decline). COPD was defined as having an FEV_1/FVC ratio <70% and FEV_1<80% of predicted, similar to GOLD stage 2 "clinically significant COPD".[30] Postbronchodilator tests were not performed because the subjects underwent methacholine tests of bronchial hyperreactivity, so the definition of COPD was based on prebronchodilator measurements.

Twenty-two centres used the same spirometer in ECRHS I and II, mostly with updated software on the second occasion. Two centres used a SensorMedics dry spirometer on one occasion (SensorMedics, Yorba Linda, California, USA) and a Jaeger Masterscope (Würzburg, Germany) on the other. Two used a Jaeger Pneumotach at each survey, but not the same instrument. A fifth used a SensorMedics spirometer and SensorMedics Vmax 22. None of these differences in equipment led to heterogeneity in change in lung function compared with other centres. However, in one centre (Melbourne) a Pneumotach was used in ECRHS I and a rolling seal spirometer (SensorMedics) in ECRHS II, resulting in an apparent increase in lung function; thus only data from the first survey were used. Measurements in participants aged 20–26 years were from ECRHS I, measurements at age 26–44 years were from both surveys and measurements at age 44–56 years were from ECRHS II.

Table 1 Frequency (%) of all childhood factors registered in ECRHS I and association of each factor with adult forced expiratory volume in 1 s (FEV_1)†

	Men		Women	
	%	Adjusted difference in FEV_1‡ (ml) (95% CI)	%	Adjusted difference in FEV_1‡ (ml) (95% CI)
Maternal asthma	5.3	−74.5 (−133 to −16.3)*	7.2	−44.0 (−79.3 to −8.6)*
Paternal asthma	5.7	−113 (−169 to −56.3)*	6.4	−69.6 (−107 to −31.8)*
Maternal atopy	17.1	7.8 (−28.0 to 43.5)	22.6	−2.7 (−25.1 to 19.7)
Paternal atopy	12.8	−14.0 (−54.5 to 26.4)	16.7	−12.5 (−38.1 to 13.1)
Childhood asthma	4.1	−290 (−352 to −227)*	2.9	−186 (−239 to −133)*
Severe respiratory infection <5 years	9.5	−108 (−152 to −63.2)*	10.8	−50.6 (−80.5 to −20.6)*
Maternal smoking	24.1	−51.4 (−82.5 to −20.3)*	25.9	−28.3 (−50 to −6.7)*
Paternal smoking	66.3	−19.6 (−47.3 to 8.0)	65.5	−4.4 (−24.1 to 15.3)
Number of siblings				
0	10.8		10.0	
1	30.6	19.2 (−26.0 to 64.4)	30.6	15.2 (−17.5 to 47.9)
2	25.4	26.7 (−20.3 to 73.6)	25.4	25.5 (−8.2 to 59.1)
3	15.3	18.4 (−33.4 to 70.1)	15.3	−0.1 (−36.9 to 36.7)
≥4	18.0	9.6 (−40.8 to 60.0)	18.8	8.1 (−27.8 to 44.1)
Order of birth				
1st	42.2		39.9	
2nd	29.7	12.0 (−18.6 to 42.6)	29.7	19.0 (−2.8 to 40.8)
3rd	14.5	33.2 (−5.9 to 72.3)	16.4	18.5 (−8.1 to 45.1)
>3rd	13.6	−8.2 (−48.3 to 32.0)	14.0	21.4 (−7.1 to 49.7)
Day care	48.6	−10.8 (−39.1 to 17.5)	46.0	5.8 (−14.6 to 26.2)
Pets				
No pet	37.7		36.2	
Cat	16.6	1.5 (−37.1 to 40.1)	18.0	31.3 (4.6 to 58)
Dog	18.2	−11.6 (−48.8 to 25.6)	16.8	8.1 (−18.9 to 35.1)
Cat and dog	27.5	13.4 (−20.3 to 47.1)	29.0	28.3 (4.6 to 52)
Season of birth				
Spring	25.9		26.5	
Summer	24.4	8.4 (−27.5 to 44.2)	24.9	8.4 (−16.8 to 33.5)
Autumn	23.9	8.1 (−28.0 to 44.2)	22.9	19.1 (−6.6 to 44.8)
Winter	25.8	42.0 (6.7 to 77.3)	25.8	3.6 (−21.3 to 28.5)

Analyses include 8201 measurements in men and 8631 measurements in women with complete data.

*$p \leqslant 0.01$.

†As measured in ECRHS I and ECRHS II.

‡Difference in FEV_1 between subjects with and without childhood factor as analysed in separate models and adjusted for smoking status, age at completed education, social class, age, height and centre.

Table 2 Associations of adult forced expiratory volume in 1 s (FEV$_1$)* with (A) individual childhood disadvantage factors and (B) the number of childhood disadvantage factors

	Men		Women	
	Adjusted difference in FEV$_1$† (ml) (95% CI)	p Value	Adjusted difference in FEV$_1$† (ml) (95% CI)	p Value
(A)				
Baseline FEV$_1$ (ml)‡	4383		3191	
Maternal asthma	−49.2 (−111.6 to 13.3)	0.123	−24.7 (−61.9 to 12.5)	0.193
Paternal asthma	−102 (−161 to −43.2)	<0.001	−58.2 (−96.9 to −19.6)	0.003
Childhood asthma	−288 (−360 to −216)	<0.001	−147 (−204 to −89.0)	<0.001
Severe respiratory infection <5 years	−70.1 (−117.1 to −23.2)	0.003	−28.2 (−59.5 to 3.1)	0.077
Maternal smoking	−44.5 (−77.9 to −11.2)	0.009	−30.5 (−53.4 to −7.6)	0.009
(B)				
Baseline FEV$_1$ (ml)‡	4372		3198	
Number of childhood disadvantage factors				
1	−58.0 (−87.0 to −29.1)	<0.001	−48.9 (−68.9 to −28.8)	<0.001
2	−201 (−253 to −149)	<0.001	−78.4 (−113 to −43.5)	<0.001
≥3	−274 (−395 to −154)	<0.001	−208 (−292 to −124)	<0.001
For comparison§				
Adult smoking status				
Ex	2.0 (−28.5 to 32.4)	0.900	29.7 (8.8 to 50.6)	0.005
Current <10 cig/day	−45.8 (−81.0 to −10.6)	0.011	−6.7 (−30.4 to 17.1)	0.583
Current 10–20 cig/day	−77.0 (−114 to −40.5)	<0.001	−16.5 (−42.6 to 9.6)	0.215
Current >20 cig/day	−112 (−149 to −74.9)	<0.001	−75.6 (−105 to −45.8)	<0.001

Analyses include 8201 measurements in men and 8631 measurements in women with complete data.
*As measured in ECRHS I and ECRHS II.
†Difference in FEV$_1$ (A) between subjects with and subjects without childhood factor when adjusting for other childhood factors in the table and (B) between subjects with a specific number of childhood factors and subjects with zero childhood factors. Adjusted for smoking status, age at completed education, social class, age, height and centre.
‡Baseline FEV$_1$ in never-smoking, high education, professional subjects of median age and median height with none of the childhood disadvantage factors.
§Estimates for adult smoking are presented in order to enable comparison of estimates. The estimates are from model B, but are practically identical in model A.

Smoking and covariates

Smokers were categorised as never-, ex- and current smokers; current smokers were further categorised based on the number of cigarettes smoked daily (<10, 10–20, ≥20). Height and weight were measured before spirometry and body mass index (BMI) was calculated from these as weight/height^2. Age when completing formal education defined "education". The last job in the occupational history defined social class. "Current adult asthma" was defined as asthma attacks during the last 12 months and/or current asthma medication. The question "Have you ever had asthma?" defined "ever asthma". "Wheeze" was defined as wheezing/whistling in the chest during the last 12 months when not having a cold. Allergen-specific IgEs were measured using the Pharmacia CAP system. Assays for allergen-specific IgE were considered positive when exceeding 0.35 kU/l. Atopy was defined as specific IgE to cat dander, house dust mite (*Dermatophagoides pteronyssinus*), timothy grass and/or *Cladosporium herbarum*.

Statistical analysis

The association of each childhood factor with adult FEV$_1$ and FVC was analysed using generalised estimating equation (GEE) models, allowing for dependency between two lung function measurements of the same individual. Adjustments were made for age, height, smoking, education, social class and centre using information about height and social class from ECRHS I and information about age, smoking and education from the same survey as the lung function measurement. Similar models were used to analyse the mutually adjusted associations between lung function and the childhood factors significantly (p≤0.01) associated with FEV$_1$ in both men and women, and the

associations of lung function with number of childhood disadvantage factors.

FEV$_1$ by age curves were fitted using generalised additive models (GAM) with adjustment for sex, height and smoking.

The associations of childhood factors with lung function decline were tested using mixed effects linear regression models with adjustment for FEV$_1$ at baseline, mid age, mid age^2, height, difference in BMI, mid BMI, sex, the interaction between sex and change in BMI, smoking at ECRHS II and centre adjusted for as a random effect due to heterogeneity across centres.[30] Men and women were analysed together as the power for analysis of lung function decline was limited in this relatively young population and there were not significant interactions by gender.

Associations of each childhood factor and of the number of childhood factors with COPD were analysed using GEE models for binary data, allowing for dependency between two lung function measurements in the same individual and adjusting for age, height, smoking, education, social class and country.

RESULTS

The level of FEV$_1$ and decline in FEV$_1$ per year of follow-up for men and women and according to all early life factors are given in table 1 in the online supplement. The adjusted associations of each childhood factor with adult FEV$_1$ are shown in table 1. Maternal asthma, paternal asthma, childhood asthma, respiratory infections and maternal smoking were associated with adult FEV$_1$ in both men and women (p≤0.01, table 1); these factors defined "childhood disadvantage".

Childhood disadvantage was highly prevalent in the population; 40% of all subjects had one or more such factors including

Figure 1 Forced expiratory volume in 1 s (FEV$_1$) by age according to number of childhood disadvantage factors in (A) men and (B) women (adjusted for smoking and height); in (C) never-smokers and (D) current smokers (adjusted for sex and height); and in (E) non-symptomatic subjects and (F) subjects who had never had asthma (childhood asthma excluded from childhood disadvantage factors) (adjusted for smoking, sex, and height). The curves were fitted using generalised additive models, based on FEV$_1$ measurements from both ECRHS I and ECRHS II for the age range 26–44 years, only ECRHS I measurements at ages 20–26 years and only ECRHS II measurements at age 45–56 years.
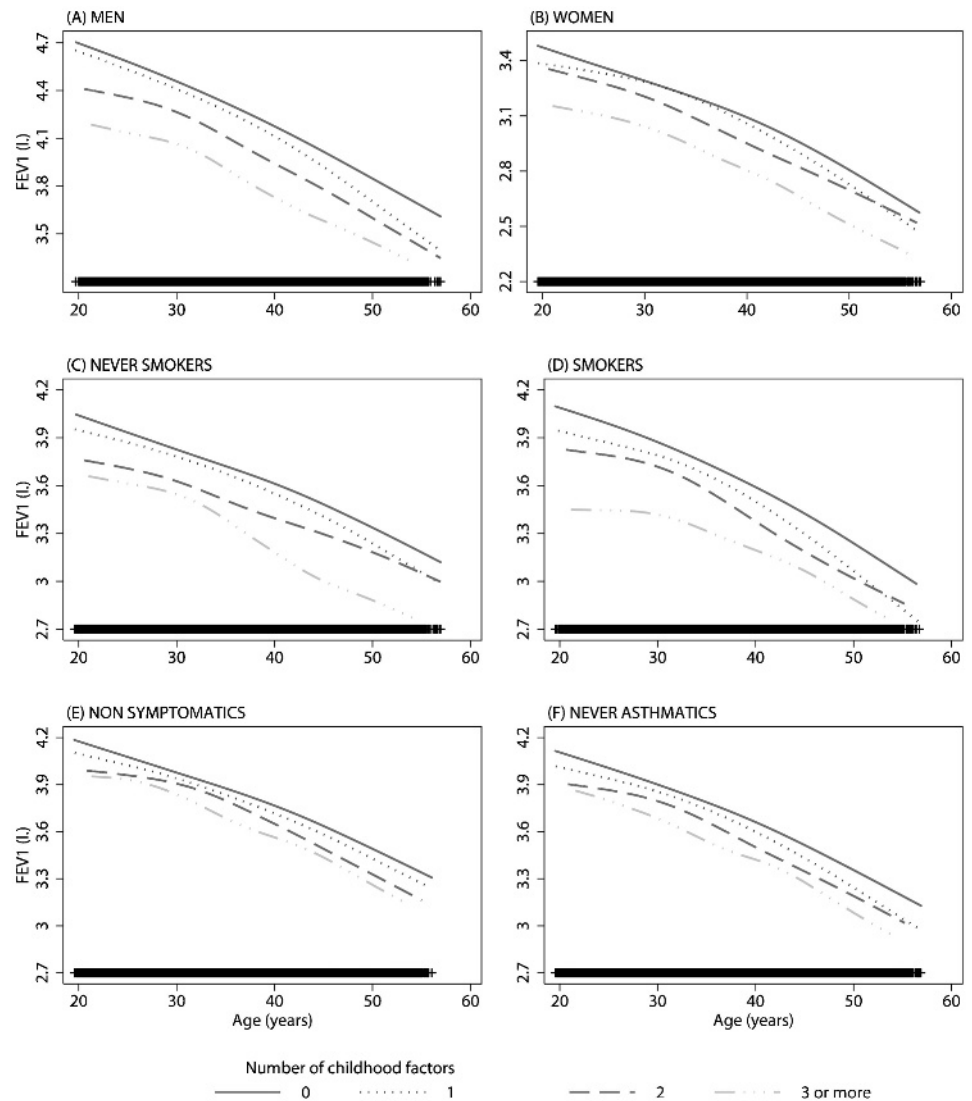
32% with one factor, 7.4% with two factors and 1.2% with three or more factors. Population characteristics varied little with childhood disadvantage while adult asthma, wheeze and atopy were increasingly prevalent with a higher number of childhood disadvantage factors (see table 2 in online supplement).

When mutually adjusting for other childhood disadvantage factors (table 2), the associations of paternal asthma, childhood asthma and maternal smoking with FEV$_1$ were practically unchanged and remained highly significant. The estimates for each childhood factor were comparable to or larger than the estimate for smoking 10–19 cigarettes daily. FEV$_1$ was consecutively lower with a higher number of childhood disadvantage factors in both men and women. Having two or more childhood disadvantage factors (8.6%) was almost as common in the population as heavy smoking (10.4%) and associated with a larger lung function deficit. Adjustment for current respiratory symptoms, asthma or atopy did not alter this conclusion (see table 3 in online supplement). Lower FEV$_1$ in subjects with one or more childhood disadvantage factors (men: 95 ml (95% CI 67 to 124); women: 60 ml (95% CI 40–80)) was consistent between centres (men: $p_{heterogeneity} = 0.34$; women: $p_{heterogeneity} = 0.24$; fig 1 in online supplement). When excluding subjects with childhood asthma (childhood disadvantage thus consisting of four factors), the effects of childhood disadvantage on adult lung

function were still highly significant and stronger than those of smoking (see table 4a in online supplement).

FEV$_1$ became lower with increasing childhood disadvantage (fig 1), which was similar for all ages. The pattern was similar for men and women (fig 1A and B) and for never-smokers and current smokers (fig 1C and D). No significant interaction with gender or smoking was detected (p>0.1). The findings were similar when subjects reporting current respiratory symptoms and/or asthma were excluded (fig 1E) and when subjects who had ever had asthma were excluded (fig 1F).

FVC was significantly lower in men and women with two childhood disadvantage factors and decreased significantly in subjects with an increasing number of childhood disadvantage factors (table 3). The association of childhood disadvantage with FVC was substantially weaker than that observed for FEV$_1$.

The decline in FEV$_1$ was 2 ml (95% CI 0.4 to 3.6) larger per year in subjects with one childhood disadvantage factor, 3.8 ml (95% CI 1.0 to 6.6) larger in those with two factors and 2.2 ml (95% CI −4.8 to 9.2) larger in those with ≥3 factors; the decline increased with an increasing number of childhood disadvantage factors (table 4). For comparison, smoking 10–20 cigarettes daily was associated with a 4 ml larger decline in lung function per year (table 4). When subjects with childhood asthma were excluded the findings were similar (see table 4b in the online

Table 3 Associations of adult forced vital capacity (FVC)* with (A) individual childhood disadvantage factors and (B) the number of childhood disadvantage factors

	Men (N = 8201)		Women (N = 8633)	
	Adjusted difference in FVC† (ml) (95% CI)	p Value	Adjusted difference in FVC† (ml) (95% CI)	p Value
(A)				
Baseline FVC (ml)‡	5347.3		3838.7	
Maternal asthma	2.0 (−70.8 to 74.7)	0.957	19.0 (−25.1 to 63.1)	0.398
Paternal asthma	−21.5 (−90.4 to 47.3)	0.540	−44.8 (−90.7 to 1.0)	0.055
Childhood asthma	−47.0 (−130.9 to 36.9)	0.272	−119.6 (−188.0 to −51.2)	0.001
Severe respiratory infection before 5 years	−37.5 (−92.3 to 17.2)	0.179	−31.0 (−68.2 to 6.1)	0.101
Maternal smoking	−7.0 (−45.9 to 31.9)	0.724	−8.8 (−36.0 to 18.4)	0.524
(B)				
Baseline FVC (ml)‡	5341.6		3840.4	
Number of childhood factors				
1	−6.4 (−39.9 to 27.1)	0.709	−24.4 (−48.0 to −0.8)	0.043
2	−60.0 (−120.0 to −0.1)	0.050	−44.8 (−85.9 to −3.6)	0.033
3	−64.6 (−204.2 to 75.0)	0.364	−177.5 (−276.4 to −78.6)	<0.001
For comparison:				
Adult smoking status				
Former	34.6 (−2.5 to 71.7)	0.067	55.8 (30.1 to 81.4)	<0.001
Current <10 cig/day	−25.4 (−69.0 to 18.2)	0.253	14.0 (−15.5 to 43.5)	0.352
Current 10–20 cig/day	−15.8 (−61.0 to 29.5)	0.495	37.7 (5.1 to 70.2)	0.023
Current >20 cig/day	−71.9 (−117.2 to −26.5)	0.002	−12.9 (−50.1 to 24.3)	0.497

Analyses include 8201 measurements in men and 8633 measurements in women with complete data.
*As measured in ECRHS I and ECRHS II.
†Difference in FVC (A) between subjects with and subjects without childhood factor when adjusting for other childhood factors in the table and (B) between subjects with a specific number of childhood factors and subjects with zero childhood factors. Adjusted for smoking status, age at completed education, social class, age, height and centre.
‡Baseline FVC in never-smoking, high education, professional subjects of median age and median height with none of the childhood disadvantage factors.
§Estimates for adult smoking are presented in order to enable comparison of estimates. The estimates are from model B, but are practically identical in model A.

supplement). Adjustment for current respiratory symptoms, asthma or atopy did not alter the findings (data not given).

Childhood asthma and paternal asthma were significantly associated with COPD (table 5). COPD increased with increasing childhood disadvantage in both men and women (table 5). The associations of COPD with childhood disadvantage were at least as strong as those with heavy smoking (table 5). When subjects with childhood asthma were excluded, COPD was still significantly associated with 2–3 childhood disadvantage factors and with an increasing number of factors, but the associations were weaker (see table 4c in online supplement).

DISCUSSION

This analysis of a large multicentre population indicates that adult lung function and susceptibility to COPD is partly determined early in life, and that the impact of childhood disadvantage appears to persist. Maternal asthma, paternal asthma, childhood asthma, severe respiratory infections before the age of 5 years and maternal smoking were associated with a lower adult FEV_1 level, and having any one or more of these factors constituted a considerable disadvantage with regard to adult lung function and COPD. Subjects with an increasing number of childhood disadvantage factors had an increasingly lower level of FEV_1 in adult life, a slightly larger decline in FEV_1 and the prevalence of COPD was substantially increased. The impairment of FEV_1 persisted up to the maximum age in our study population (56 years) and no catch-up was detected. Childhood disadvantage was as common in the population as current smoking, and showed an equally large impact on lung function and COPD and a slightly smaller impact on lung function decline. These findings were similar for men and

women, smokers and non-smokers, subjects who had never had asthma and non-symptomatic subjects, and were consistent across different geographical areas.

To our knowledge, no other studies have attempted to assess the overall impact of early life origins on adult lung function and COPD. Studies on single factors—in particular on childhood asthma,[4][27] lower respiratory infections[5][21–23] and maternal smoking[18–20]—mostly agree that the respective factors affect the level of lung function in early adulthood but not the decline in lung function. The lack of association between the individual factors and a decline in lung function agrees with our findings; when we considered each risk factor separately there were only minor effects. However, when attempting to describe overall early life disadvantage by counting the number of disadvantage factors, a larger decline was revealed. Knowledge about early life origins of COPD is scarce.[13] Our study has the advantages of being very large, including older subjects than most previous studies and investigating representative populations from many countries.

The main limitation of the present study is the retrospective nature of the information about early life. The accuracy of recalling childhood asthma by adults may be related to current symptoms.[31] However, when excluding subjects with current symptoms or asthma, our findings remained unchanged. Also, in our study the outcome measures were objective and not yet perceived; this made differential recall bias less likely. Finally, it seems unlikely that recall error should cause spurious results in a consistent pattern across centres. A previous analysis revealed that adults reported important childhood events with high consistency regardless of symptom status.[32] However, some random misclassification of early life factors due to non-differential recall error is likely and will have attenuated the

Table 4 Associations of decline in adult forced expiratory volume in 1 s (FEV$_1$)* with (A) individual childhood disadvantage factors and (B) the number of childhood disadvantage factors in 5608 subjects with complete data

	Adjusted decline in FEV$_1$ (ΔFEV$_1$†, ml/year) (95% CI)	p Value
(A)		
Baseline decline (ml/year)‡	−23.2	
Maternal asthma	−0.5 (−3.7 to 2.7)	0.770
Paternal asthma	−2.1 (−5.3 to 1.0)	0.186
Childhood asthma	−5.9 (−10.7 to −1.2)	0.013
Severe respiratory infection <5 years	−1.1 (−3.6 to 1.4)	0.385
Maternal smoking	−1.3 (−3.2 to 0.6)	0.175
(B)		
Baseline decline (ml/year)‡	−23.4	
Number of childhood factors		
1	−2.0 (−3.6 to −0.4)	0.014
2	−3.8 (−6.6 to −1.0)	0.009
⩾3	−2.2 (−9.2 to 4.8)	0.542
p for trend	0.003	
For comparison:		
Adult smoking status		
Ex	3.5 (1.8 to 5.3)	<0.001
Current <10 cig/day	−0.7 (−3.7 to 2.3)	0.639
Current 10–20 cig/day	−4.0 (−6.9 to −1.1)	0.006
Current >20 cig/day	−9.5 (−11.9 to −7.0)	<0.001

*Decline in forced expiratory volume in 1 s in ml per year of follow-up (FEV$_1$ in ECRHS II minus FEV$_1$ in ECRHS I).
†Difference in decline in FEV$_1$ in ml per year of follow-up (A) between subjects with and subjects without childhood factor when adjusting for other childhood factors in the table and (B) between subjects with a specific number of childhood factors and subjects with zero childhood factors. Adjusted for FEV$_1$ at baseline, mid age, mid age^2, height at ECRHS II, change in BMI, mid BMI, sex, interaction between sex and change in BMI, smoking, age at completed education, social class and centre as random effect.
‡Baseline decline in FEV$_1$ per year of follow-up in never-smoking, high education, professional subjects of median age, median height and median BMI with none of the childhood disadvantage factors.
§Estimates for adult smoking are presented in order to enable comparisons of estimates. The estimates are from model B, but are practically identical for model A.

associations, so the observed estimates may underestimate the true effects. Another problem of this study was a lack of information on potentially important factors such as childhood exposure to air pollution and childhood nutrition, which may also have contributed to an underestimate of the true importance of early life disadvantage. Only prebronchodilator spirometric measures were available. The findings were consistent when subjects who had ever had diagnosed asthma or currently had respiratory symptoms were excluded. However, the findings might relate to asymptomatic bronchoconstriction rather than to fixed airway damage; this should be investigated in future studies.

There are several possible mechanisms by which childhood disadvantage might influence adult lung function and development of COPD. Early life factors could reduce lung growth in utero and in early childhood and prevent individuals from ever reaching the potential maximum lung function level, as suggested by the observed associations with FEV$_1$ and FVC. Early life environment might further influence physiological factors directly related to lung function throughout life (ie, by causing persistent inflammation).[33] This could possibly explain the persistence of effects of childhood disadvantage in adulthood and the larger decline in lung function. Both lung growth impairment and persistent inflammation might explain the demonstrated higher risk of COPD in subjects with childhood disadvantage. Finally,

early life factors might increase susceptibility to subsequent risk factors. In our study smoking did not interact with childhood disadvantage, so no increased vulnerability to smoking among subjects with childhood disadvantage was found.

One may question whether asthma was a mediator for the effects of childhood disadvantage on adult lung function and COPD. Lung function during childhood and adolescence is impaired in children with asthma, probably due to chronic inflammation and reduced lung growth.[26] The role of childhood asthma in lung function decline is controversial,[4] while it appears convincing that adult asthma is, after smoking, the most important risk factor for low FEV$_1$.[34 35] In the present study, childhood asthma showed the strongest associations with level of lung function when analysing each childhood disadvantage factor separately. However, the results remained practically unchanged when childhood asthma was excluded (see fig 2F and online tables 4A–C), and the observed associations with FEV$_1$, decline in FEV$_1$ and COPD were independent of current adult asthma (see fig 2E and online table 3). Thus, the effects of childhood disadvantage on adult lung function and COPD in this study were not mediated by asthma. On the other hand, the effects of early life factors on adult asthma may be a consequence of the impact on lung function development.

The definition of early life disadvantage in the present study implies a combination of genetic and environmental factors. A possible genetic effect might be captured by factors such as parental asthma. However, mother, father and child also share a common environment. While childhood asthma in itself may influence lung function, childhood asthma is also a result of genetic susceptibility. The environmental and genetic contributions of these factors cannot therefore easily be separated.

In conclusion, this study suggests that adult respiratory health to a large extent originates early in life. In the struggle to prevent COPD, intervention in early life in addition to smoking prevention might help abate the ongoing COPD epidemic. Programmes focusing on maternal smoking in pregnancy and the perinatal period are likely to be as beneficial as programmes reducing active smoking for decades in other periods of life. Treatment of childhood asthma might have long-term effects on COPD,[36] and one may speculate whether vaccination against lower respiratory tract infections might also promote adult respiratory health. With regard to secondary prevention, follow-up of subjects with early life disadvantage should focus on special preventive measures against known environmental determinants for COPD. For instance, smoking prevention campaigns among teenagers could include determination of risk profiles and increase efforts in subjects with known childhood disadvantage. Given that almost half of the investigated western populations had one or more identifiable childhood disadvantage factors, this study implies that any improvement in early life environment may have large beneficial effects in the primary prevention of COPD.

Table 5 Associations of chronic obstructive pulmonary disease (COPD)* with (A) individual childhood disadvantage factors and (B) with the number of childhood disadvantage factors

	Men		Women	
	OR† (95% CI)	p Value	OR† (95% CI)	p Value
(A)	1 (reference)		1 (reference)	
Maternal asthma	1.26 (0.56 to 2.82)	0.576	1.55 (0.73 to 3.31)	0.255
Paternal asthma	2.69 (1.53 to 4.74)	0.001	2.94 (1.60 to 5.41)	0.001
Childhood asthma	10.48 (6.10 to 18.03)	<0.001	3.74 (1.55 to 9.02)	0.003
Severe respiratory infection before 5 years	1.34 (0.77 to 2.35)	0.303	0.69 (0.31 to 1.53)	0.362
Maternal smoking	1.41 (0.89 to 2.25)	0.143		
(B)				
Number of childhood factors				
0 (reference)	1 (reference)		1 (reference)	
1	1.71 (1.10 to 2.64)	0.017	1.62 (1.01 to 2.60)	0.046
2	5.23 (3.14 to 8.73)	<0.001	2.41 (1.26 to 4.61)	0.008
3	6.32 (2.35 to 16.98)	<0.001	7.16 (2.75 to 18.64)	<0.001
For comparison				
Adult smoking status				
Former	2.44 (1.39 to 4.27)	0.002	1.00 (0.51 to 1.94)	0.999
Current <10 cig/day	2.50 (1.27 to 4.91)	0.008	0.62 (0.20 to 1.88)	0.398
Current 10–20 cig/day	2.16 (1.07 to 4.34)	0.031	2.32 (1.16 to 4.66)	0.018
Current >20 cig/day	3.70 (2.05 to 6.69)	<0.001	3.82 (2.04 to 7.13)	<0.001

Analyses include 8201 measurements in men and 8633 measurements in women with complete data.
*COPD defined as forced expiratory volume in 1 s/forced vital capacity (FEV_1/FVC) ratio <0.70 and FEV_1 <80% predicted; based on prebronchodilator lung function measurements from ECRHS I and ECRHS II.
†Odds ratio (OR) for COPD (A) comparing subjects with and without each childhood factor when adjusting for other childhood factors in the table and (B) comparing subjects with a specific number of childhood factors with subjects with zero childhood factors. Adjusted for smoking status, age completed education, social class, age, height and centre.
‡Estimates for adult smoking are presented in order to enable comparisons of estimates. The estimates are from model B, but are practically identical for model A.

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On-line repository

"Early life origins of chronic obstructive pulmonary disease"

Svanes C et al

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Legends to figures

On-line repository, figure 1. Meta-analysis of the association of adult FEV_1 with one or more childhood disadvantage factors by centre in (A) men and (B) women, adjusted for smoking status, age and height. Boxes shows adjusted difference in FEV_1 in reference to those with 0 childhood disadvantage factors, horizontal lines show 95%CI, diamond shows combined estimate for all centres with 95%CI. Analyses include 8201 measurements in men and 8631 measurements in women with complete data, as measured in ECRHS I and ECRHS II.

On-line repository, table 1. Adult FEV$_1$ and decline in FEV$_1$ per year of follow-up in men and women, according to all childhood factors registered in ECRHS I.

| | | FEV$_1$* | | | | decline in FEV$_1$† | | | |
| | | MEN | | WOMEN | | MEN | | WOMEN | |
		number ‡	Mean FEV$_1$(l)	number ‡	Mean FEV$_1$(l)	number ‡	Mean FEV$_1$(l)	number ‡	Mean FEV$_1$(l)
Maternal asthma	No	9290	4.26	9516	3.15	2975	-32.6	3042	-24.7
	Yes	522	4.17	748	3.06	160	-30.4	234	-28.1
Paternal asthma	No	9064	4.26	9276	3.15	2910	-32.6	2957	-24.5
	Yes	553	4.09	649	3.01	173	-32.7	214	-26.9
Maternal atopy	No	7724	4.24	7712	3.13	2499	-32.1	2497	-24.3
	Yes	1619	4.31	2313	3.18	477	-32.9	703	-26.5
Paternal atopy	No	8074	4.24	7994	3.14	2589	-31.9	2563	-24.4
	Yes	1181	4.29	1633	3.16	378	-35.9	519	-26.3
Childhood asthma	No	9808	4.26	10196	3.14	3154	-32.3	3263	-24.9
	Yes	422	4.00	315	3.04	118	-35.4	89	-20.7
Severe respiratory infection <5 yrs	No	8713	4.26	8866	3.15	2778	-32.3	2815	-24.8
	Yes	916	4.17	1098	3.07	289	-34.7	352	-25.2
Maternal smoking	No	7657	4.25	7733	3.13	2495	-31.1	2484	-24.3
	Yes	2433	4.26	2703	3.16	733	-36.6	844	-26.5
Paternal smoking	No	3362	4.32	3556	3.19	1080	-32.9	1150	-23.7
	Yes	6531	4.22	6630	3.12	2090	-32.2	2108	-25.4
Nº of siblings:	0	1109	4.28	1060	3.16	355	-33.7	325	-26.0
	1	3136	4.33	3216	3.19	988	-32.1	1025	-23.9
	2	2590	4.27	2671	3.18	846	-31.3	850	-25.9
	3	1565	4.20	1608	3.10	517	-33.1	517	-24.3
	4 or more	1844	4.12	1966	3.04	571	-33.5	638	-25.1
Order of birth:	0	4313	4.28	4204	3.14	1393	-33.4	1340	-25.7
	1	3047	4.25	3114	3.16	979	-31.7	980	-24.7
	2	1477	4.27	1716	3.14	472	-32.3	555	-23.5
	3 or more	1396	4.15	1468	3.09	430	-31.5	473	-25.3
Day care:	No	5181	4.21	5637	3.10	1747	-34.3	1910	-27.9
	Yes	4824	4.30	4744	3.19	1445	-30.3	1406	-20.7
Pet at EC1:	No pet	3834	4.29	3779	3.16	1264	-32.7	1249	-25.7
	Cat	1734	4.24	1923	3.14	594	-33.5	647	-26.7
	Dog	1853	4.23	1776	3.14	558	-32.1	513	-22.5
	Cat&Dog	2817	4.21	3050	3.12	863	-31.6	953	-23.9
Season of birth:	Spring	2671	4.25	2785	3.13	862	-32.0	915	-25.2
	Summer	2488	4.26	2642	3.14	788	-32.2	827	-24.7
	Autumn	2457	4.24	2421	3.14	790	-31.8	779	-23.6
	Winter	2653	4.26	2707	3.15	844	-33.7	842	-26.0

* Level of forced expiratory volume in one second as measured in ECRHS I and ECRHS II
† Decline in forced expiratory volume in one second in ml per year of follow-up (FEV$_1$ in ECRHS II minus FEV$_1$ in ECRHS I).
‡ Sums (yes+no) differ due to a different number with missing information for each variable. Numbers refer to numbers of measurements for FEV$_1$ and number of individuals with two measurements for FEV$_1$ decline.

On-line repository, table 2. Characteristics of study population according to number of childhood disadvantage factors*.

		All	Number of childhood disadvantage factors			
			0	1	2	≥3
	N†	13,359	8,000	4,224	979	156
			(60%)	(32%)	(7.4%)	(1.2%)
Adult smoking status						
Never	(%)	43.4	44.0	42.4	42.8	42.3
Ex	(%)	23.8	23.9	24.0	22.9	23.3
Current <10	(%)	12.6	12.9	12.5	11.3	10.7
Current 10-20	(%)	9.7	9.4	10.3	10.3	8.4
Current>20	(%)	10.4	9.9	10.9	12.8	15.4
BMI (kg/m^2)	(median)	23.8	23.7	23.8	24.0	23.9
Height	(mean)	1.71	1.71	1.71	1.70	1.70
Age	(mean)	36.9	37.2	36.5	36.8	35.9
Age completed education						
>22 years	(%)	28.8	28.9	27.8	30.9	33.6
18-22 years	(%)	31.2	31.5	31.6	27.2	30.4
≤18 years	(%)	40.1	39.6	40.6	42.0	36.0
Social Class						
I-II Professionals	(%)	30.1	30.2	30.3	28.1	34.1
III Non-manual	(%)	18.2	18.1	18.2	19.2	17.5
III Manual	(%)	16.6	16.0	17.7	15.5	22.0
IV-V Unskilled	(%)	12.9	12.0	14.2	16.0	9.4
Unclassified	(%)	22.2	23.7	19.7	21.2	17.0
Current asthma	(%)	5.1	2.9	6.0	15.5	29.5
Current wheeze	(%)	13.1	10.1	16.0	23.1	33.8
Atopy	(%)	30.4	28.2	32.3	37.8	48.3

* Maternal asthma, paternal asthma, childhood asthma, respiratory infections, and maternal smoking constituted the childhood disadvantage factors.
† N includes number of persons with data on lung function and childhood factors. Using person-surveys gave almost identical results.

On-line repository, table 3. Full models for associations of adult FEV$_1$* with (**A**) individual childhood factors mutually adjusted for each other and (**B**) number of childhood disadvantage factors, when including adjustment for current adult asthma, wheeze and atopy. Analyses include 7435 measurements in men and 7655 measurements in women with complete data.

	MEN			WOMEN		
	Adjusted difference in FEV$_1$[†] (ml)	95% CI	p-val	Adjusted difference in FEV$_1$[†] (ml)	95% CI	p-val
A						
Baseline FEV$_1$ (ml) ‡	4401.1			3214.8		
Maternal asthma	-47.9	(-111.7, 15.8)	0.141	-15.6	(-54.1, 22.9)	0.427
Paternal asthma	-79.9	(-140.1, -19.7)	0.009	-46.8	(-86.6, -7.0)	0.021
Childhood asthma	-180.5	(-257.6, -103.3)	<0.001	-80.4	(-141.5, -19.3)	0.010
Severe respiratory infection <5 years	-67.3	(-115.4, -19.1)	0.006	-28.0	(-60.4, 4.3)	0.089
Maternal smoking	-33.7	(-67.9, 0.4)	0.053	-28.4	(-52.2, -4.6)	0.019
B						
Baseline FEV$_1$ (ml) ‡	4390.9			3222.6		
Number of childhood factors						
1	-43.9	(-73.5, -14.3)	0.004	-40.6	(-61.3, -19.9)	<0.001
2	-158.3	(-211.6, -105.0)	<0.001	-57.7	(-93.9, -21.6)	0.002
3 or more	-149.5	(-274.5, -24.5)	0.019	-137.5	(-226.2, -48.7)	0.002
For comparison:						
Adult smoking status						
Ex	9.3	(-22.4, 41.1)	0.564	31.5	(9.8, 53.2)	0.004
Current <10 cig/day	-32.4	(-69.8, 4.9)	0.089	-10.7	(-35.8, 14.3)	0.400
Current 10-20 cig/day	-64.6	(-103.0, -26.1)	<0.001	1.4	(-26.1, 28.8)	0.922
Current >20 cig/day	-103.6	(-142.8, -64.5)	<0.001	-75.5	(-107.4, -43.7)	<0.001
Age at completed education						
18-22 years	-17.3	(-45.8, 11.2)	0.233	-22.9	(-42.6, -3.1)	0.023
≤18 years	-65.7	(-97.9, -33.5)	<0.001	-49.5	(-71.9, -27.1)	<0.001
Social Class (I-II)						
III Non-manual	-37.2	(-85.3, 11.0)	0.130	-8.4	(-36.5, 19.6)	0.555
III Manual	-52.6	(-92.8, -12.3)	0.010	-29.1	(-68.4, 10.3)	0.148
IV-V Unskilled	-16.5	(-66.4, 33.4)	0.517	-9.2	(-43.2, 24.8)	0.596
Unclassified	-100.7	(-156.3, -45.1)	<0.001	-25.1	(-59.0, 8.7)	0.146
Current asthma	-208.1	(-267.0, -149.2)	<0.001	-114.6	(-150.5, -78.6)	<0.001
Current wheeze	-103.2	(-133.7, -72.7)	<0.001	-92.6	(-115.9, -69.3)	<0.001
Current atopy	-6.7	(-31.2, 17.8)	0.594	-15.8	(-34.5, 3.0)	0.101

* Forced expiratory volume in one second as measured in ECRHS I and ECRHS II.
† Difference in FEV$_1$ (***A***) between subjects with and subjects without childhood factor, when adjusting for other childhood factors in the table (***B***) between subjects with a specific number of childhood factors and subjects with zero childhood factors. Analysed using generalized estimating equations models allowing for

dependency between two lung function measurements of the same individual, and adjusting for smoking status, age at completed education, social class, current asthma, current wheeze, atopy, age, height and centre.
‡ Baseline FEV_1 in never-smoking, high education, professional, median age, median height subjects with none of the childhood disadvantage factors, and no current adult asthma, wheeze or atopy.

On-line repository, table 4a. Associations of adult FEV$_1$* with individual childhood disadvantage factors (**A**) and with number of childhood disadvantage factors (**B**); when excluding all subjects with childhood asthma and excluding childhood asthma from the childhood disadvantage factors. Analyses include 7906 measurements in men and 8395 measurements in women with complete data.

	MEN (N=7,906)			WOMEN (N= 8,395)		
	Adjusted difference in FEV$_1$[†] (ml)	95% CI	p-val	Adjusted difference in FEV$_1$[†] (ml)	95% CI	p-val
A						
Baseline FEV$_1$ (ml) ‡	4385.7			3192.5		
Maternal asthma	-53.2	(-117.1,10.7)	0.103	-32.0	(-70.3,6.2)	0.101
Paternal asthma	-77.4	(-138.3,-16.4)	0.013	-50.1	(-89.8,-10.3)	0.014
Severe respiratory infection before 5 yrs	-68.3	(-117.2,-19.5)	0.006	-32.0	(-64.4,0.4)	0.053
Maternal smoking	-41.7	(-75.3,-8.1)	0.015	-32.3	(-55.5,-9.1)	0.006
B						
Baseline FEV$_1$ (ml) ‡	4377.9			3200.2		
Number of childhood factors						
1	-44.7	(-73.9,-15.4)	0.003	-43.7	(-63.9,-23.5)	<0.001
2	-134.7	(-193.0,-76.3)	<0.001	-55.2	(-93.1,-17.4)	0.004
3	-141.3	(-335.0,52.4)	0.153	-201.0	(-329.0,-73.0)	0.002
For comparison:						
Adult smoking status						
Former	4.0	(-26.5,34.5)	0.798	28.5	(7.5,49.6)	0.008
Current <10 cig/day	-40.4	(-75.8,-5.1)	0.025	-5.8	(-29.8,18.2)	0.637
Current 10-20 cig/day	-74.8	(-111.3,-38.2)	<0.001	-17.3	(-43.6,9.0)	0.197
Current >20 cig/day	-105.0	(-142.0,-68.0)	<0.001	-77.6	(-107.6,-47.6)	<0.001

* Forced expiratory volume in one second.
† Difference in FEV$_1$ (**A**) between subjects with and subjects without childhood factor, when adjusting for other childhood factors in the table (**B**) between subjects with a specific number of childhood factors and subjects with zero childhood factors. Adjusted for smoking status, age at completed education, social class, age, height and centre.
‡ Baseline FEV$_1$ in never-smoking, high education, professional, median age, median height subjects with none of the childhood disadvantage factors.
§ Estimates for adult smoking are presented in order to enable comparison of estimates. The estimates are from model B, but are practically identical in model A.

On-line repository, table 4b. Associations of decline in adult FEV_1* with individual childhood disadvantage factors (**A**) and with number of childhood disadvantage factors (**B**) in 5498 persons with complete data, excluding all subjects with childhood asthma and excluding childhood asthma from the childhood disadvantage factors.

	adjusted difference in ΔFEV_1[†] (ml/year)	95% CI	p-val
A			
Baseline ΔFEV_1 (ml/yr) ‡	-22.9		
Maternal asthma	-0.4	(-3.7,2.8)	0.795
Paternal asthma	-2.0	(-5.2,1.2)	0.215
Severe respiratory infection < 5 yrs	-1.5	(-4.1,1.0)	0.235
Maternal smoking	-1.2	(-3.0,0.7)	0.219
B			
Baseline ΔFEV_1 (ml/yr) ‡	-23.3		
Number of childhood factors			
1	-1.7	(-3.3,-0.1)	0.037
2	-2.7	(-5.8,0.4)	0.089
3 or more	-5.9	(-16.0,4.1)	0.249
p for trend	*0.016*		
For comparison:			
Adult smoking stauts			
Former	3.4	(1.6,5.1)	<0.001
Current <10 cig/day	-1.2	(-4.2,1.8)	0.445
Current 10-20 cig/day	-4.2	(-7.1,-1.3)	0.004
Current >20 cig/day	-9.1	(-11.6,-6.6)	<0.001

* Decline in forced expiratory volume in one second in ml per year of follow-up (FEV_1 in ECRHS II minus FEV_1 in ECRHS I)

[†] Difference in decline in FEV_1 in ml per year of follow-up (*A*) between subjects with and subjects without childhood factor, when adjusting for other childhood factors in the table (*B*) between subjects with a specific number of childhood factors and subjects with zero childhood factors. Adjusted for FEV_1 at baseline, mid age, midage[2], height at ECRHS II, difference in BMI, mid BMI, smoking, age at completed education, social class and centre.

‡ Baseline decline in FEV_1 per year of follow-up in never-smoking, high education, professional, median age, median height, median BMI subjects with none of the childhood disadvantage factors.

§ Estimates for adult smoking are presented in order to enable comparisons of estimates. The estimates are from model B, but are practically identical for model A.

On-line repository, table 4c. Associations of COPD* with individual childhood disadvantage factors (**A**) and with number of childhood disadvantage factors (**B**) when excluding all subjects with childhood asthma and excluding childhood asthma from the childhood disadvantage factors. Analyses include 7905 measurements in men and 8395 measurements in women with complete data.

	MEN (N=7,905)			WOMEN (N=8,395)		
	OR[†]	95% CI	p-val	OR[†]	95% CI	p-val
(A)						
Maternal asthma	1.71	(0.72-4.04)	0.221	1.69	(0.77-3.73)	0.194
Paternal asthma	2.30	(1.15-4.61)	0.019	2.55	(1.29-5.03)	0.007
Severe respiratory infection < 5 yrs	1.52	(0.78-2.98)	0.221	0.53	(0.19-1.45)	0.216
Maternal smoking	1.35	(0.80-2.29)	0.264	1.64	(0.95-2.81)	0.075
(B)						
Number of childhood factors						
0 (ref.)	1			1		
1	1.40	(0.87-2.23)	0.164	1.61	(0.98-2.64)	0.060
2 or 3	2.54	(1.28-5.03)	0.007	2.27	(1.14-4.53)	0.020
For comparison ‡:						
Adult smoking stauts						
Former	2.77	(1.44-5.35)	0.002	1.18	(0.61-2.29)	0.631
Current <10 cig/day	3.31	(1.52-7.23)	0.003	1.03	(0.40-2.64)	0.952
Current 10-20 cig/day	3.03	(1.40-6.53)	0.005	2.41	(1.19-4.88)	0.015
Current >20 cig/day	4.42	(2.25-8.69)	<0.001	4.95	(2.71-9.05)	<0.001

* COPD defined as FEV_1/FVC ratio <0.70 and FEV_1<80% predicted, lung function measurements from ECRHS I and ECRHS II.
† Odds ratio (OR) for COPD (A) comparing subjects with and without each childhood factor, when adjusting for other childhood factors in the table (**B**) comparing subjects with a specific number of childhood factors with subjects with zero childhood factors. Adjusted for smoking status, age completed education, social class, age, height and centre.
‡ Estimates for adult smoking are presented in order to enable comparisons of estimates. The estimates are from model B, but are practically identical for model A.

South Antwerp
Antwerp city
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Galdakao
Albacete
Oviedo
Huelva
Bordeaux
Grenoble
Montpellier
Paris
Pavia
Turin
Verona
Cardiff
Ipswich
Norwich
Reykjavik
Bergen
Goteborg
Umea
Uppsala
Basel
Tartu

Combined

-300   -200   -100   0   100   200

Adjusted difference in FEV1 (ml), Men

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Norwich
Reykjavik
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Goteborg
Umea
Uppsala
Basel
Tartu

Combined

Adjusted difference in FEV1 (ml), Women

-300   -200   -100   0   100   200

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