Early life origins of chronic obstructive pulmonary disease

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ABSTRACT

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

Methods European Community Respiratory Health Survey participants aged 20-45 years, randomly selected from general populations in 29 centres, had a spirometry in 1991-93 (n=13,359) and nine years later (n=7,738). Associations of early life factors with adult FEV_1, FEV_1 decline and COPD (FEV_1/FVC ratio<70% and FEV_1<80% predicted) were analysed with Generalized 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 "childhood disadvantage". Forty percent had one or more childhood disadvantage factor, which was associated with lower FEV_1 (men: adjusted difference 95ml[95%CI=67-124]; women (60ml[40-80]). FEV_1 decreased with increasing childhood disadvantage (≥3 factors men: 274ml[154-395], women: 208ml[124-292]. Childhood disadvantage was associated with larger FEV_1 decline (one factor 2.0ml [0.4-3.6] per year; two factors 3.8ml [1.0-6.6]; ≥3 factors 2.2ml[-4.8-9.2]). COPD increased with increasing childhood disadvantage (one factor men: OR=1.7[95%CI=1.1-2.6], women: 1.6[1.01-2.6]; ≥3 factors: men: 6.3[2.4-17], women: 7.2[2.8-19]). These findings were consistent between centres, and when excluding subjects with asthma.

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

INTRODUCTION

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 age two years[7, 8]. Thereafter growth and functional development of the bronchial tree and the alveoli continues until a plateau phase is reached, by the end of the adolescence in women[9] and in the mid-twenties 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].

The present study addresses to what extent adult lung function and COPD is already determined in childhood, as 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 adult lung function level, 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 multi-cultural population from centres with wide variations in prevalence of COPD[12], including 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 1991-93. Subjects included were 13,359 (6,624 men and 6,735 women) (85% of the eligible) from random samples from 29 centres with lung function at ECRHS I. Among them, 7,738 (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 (inter-quartile range 8.3-9.5 years), the age range at follow-up was 26-56 years. The full protocol can be found at www.ecrhs.org. Ethical approval was obtained for each centre from the appropriate institutional or regional ethics committee, and written informed consent was obtained from each participant.

Design

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 including 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 age 10 years. Factors associated with adult FEV_1 in both men and women at a significance level of $p \leq 0.01$ 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 forced expiratory volume in one second (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 were expressed per year of follow-up (ECRHS II value minus ECRHS I value, a negative value represents decline). COPD was defined as having a FEV_1/FVC ratio<70% and FEV_1<80% of predicted, similar to GOLD stage 2 "clinically significant COPD" [30]. Post-bronchodilator tests were not performed because the subjects underwent methacholine tests of bronchial hyperreactivity, thus, definition of COPD was based on pre-bronchodilator measurements.

Twenty-two centres used the same spirometer in ECRHS I and II, mostly with updated software at the second occasion. Two centres used SensorMedics dry spirometer at one occasion, Jaeger Masterscope at the other. Two used Jaeger Pneumotach at each survey, but not the same instrument. A fifth used SensorMedics spirometer and SensorMedics Vmax 22. None of these differences in equipment led to heterogeneity in lung function change compared to other centres. However one centre (Melbourne) used Pneumotach in ECRHS I and a rolling seal spirometer (Sensor-Medics, Yorba linda, California, USA) 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 from both surveys and measurements at age 44-56 years from ECRHS II.

Smoking and covariates

Smoking was categorised as never-, ex- and current smoking; current smokers were further categorised based on number of cigarettes smoked daily (<10, 10-20, ≥20). Height and weight was measured before spirometry; 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 chest during 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 equations (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 ($p \leq 0.01$) 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, midage^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 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 number of childhood factors with COPD were analysed using generalised estimating equations (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

Level of FEV_1 and decline of FEV_1 per year follow-up for men and women and according to all early life factors are given in the online repository (online repository, table 1). The adjusted associations of each childhood factor with adult FEV_1 are presented 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 at $p \leq 0.01$ (table 1); these factors defined "childhood disadvantage".

Table 1. Frequency (%) of all childhood factors registered in ECRHS I, and association of each factor with adult FEV_1†. Analyses include 8201 measurements in men and 8631 measurements in women with complete data.

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

* p-value ≤0.01
† Forced expiratory volume in one second, 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.

Childhood disadvantage was highly prevalent in the population; 40% of all subjects had one or more such factor including 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 (online repository, table 2).

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 (online repository, table 3). Lower FEV_1 in subjects with one or more childhood disadvantage factors (men: 95ml [95%CI=67 –124]; women 60ml [40-80]) was consistent between centres (men: $p_{heterogeneity}=0.34$; women: $p_{heterogeneity}=0.24$; online repository, figure 1). 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 (online repository, table 4a).

Table 2. Associations of adult FEV_1* with individual childhood disadvantage factors (A) and with number of childhood disadvantage factors (B). Analyses include 8201 measurements in men and 8631 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) ‡	*4383*			*3191*		
Maternal asthma	-49.2	(-111.6, 13.3)	0.123	-24.7	(-61.9, 12.5)	0.193
Paternal asthma	-102	(-161, -43.2)	<0.001	-58.2	(-96.9, -19.6)	0.003
Childhood asthma	-288	(-360, -216)	<0.001	-147	(-204, -89.0)	<0.001
Severe respiratory infection <5 years	-70.1	(-117.1, -23.2)	0.003	-28.2	(-59.5, 3.1)	0.077
Maternal smoking	-44.5	(-77.9, -11.2)	0.009	-30.5	(-53.4, -7.6)	0.009
B						
Baseline FEV_1 (ml) ‡	*4372*			*3198*		
Number of childhood disadvantage factors						
1	-58.0	(-87.0, -29.1)	<0.001	-48.9	(-68.9, -28.8)	<0.001
2	-201	(-253, -149)	<0.001	-78.4	(-113, -43.5)	<0.001
3 or more	-274	(-395, -154)	<0.001	-208	(-292, -124)	<0.001
For comparison§						
Adult smoking status						
Ex	2.0	(-28.5, 32.4)	0.900	29.7	(8.8, 50.6)	0.005
Current <10 cig/day	-45.8	(-81.0, -10.6)	0.011	-6.7	(-30.4, 17.1)	0.583
Current 10-20 cig/day	-77.0	(-114, -40.5)	<0.001	-16.5	(-42.6, 9.6)	0.215
Current >20 cig/day	-112	(-149, -74.9)	<0.001	-75.6	(-105, -45.8)	<0.001

* 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. 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.

FEV_1 was consecutively lower with increasing childhood disadvantage (figure 1), similar for all ages. The pattern was similar for men and women (figure 1A and B), never-smokers and current smokers (figure 1C and D). Significant interaction with gender or smoking was not detected ($p>0.1$). The findings were similar when excluding subjects reporting current respiratory symptoms and/or asthma (figure 1E) and when excluding subjects who ever had asthma (figure 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 strengths of the associations were crudely comparable to those of smoking. The association of childhood disadvantage with FVC was substantially weaker than that observed for FEV_1.

Table 3. Associations of adult FVC* with individual childhood disadvantage factors (**A**) and with number of childhood disadvantage factors (**B**). Analyses include 8201 measurements in men and 8633 measurements in women with complete data.

	MEN (N=8,201)			**WOMEN (N=8,633)**		
	Adjusted difference in FVC† (ml)	**95% CI**	**p-val**	**Adjusted difference in FVC† (ml)**	**95% CI**	**p-val**
A						
Baseline FVC (ml) ‡	5347.3			3838.7		
Maternal asthma	2.0	(-70.8,74.7)	0.957	19.0	(-25.1,63.1)	0.398
Paternal asthma	-21.5	(-90.4,47.3)	0.540	-44.8	(-90.7,1.0)	0.055
Childhood asthma	-47.0	(-130.9,36.9)	0.272	-119.6	(-188.0,-51.2)	0.001
Severe respiratory infection before 5 yrs	-37.5	(-92.3,17.2)	0.179	-31.0	(-68.2,6.1)	0.101
Maternal smoking	-7.0	(-45.9,31.9)	0.724	-8.8	(-36.0,18.4)	0.524
B						
Baseline FVC (ml) ‡	5341.6			3840.4		
Number of childhood factors						
1	-6.4	(-39.9,27.1)	0.709	-24.4	(-48.0,-0.8)	0.043
2	-60.0	(-120.0,-0.1)	0.050	-44.8	(-85.9,-3.6)	0.033
3	-64.6	(-204.2,75.0)	0.364	-177.5	(-276.4,-78.6)	<0.001
For comparison:						
Adult smoking stauts						
Former	34.6	(-2.5,71.7)	0.067	55.8	(30.1,81.4)	<0.001
Current <10 cig/day	-25.4	(-69.0,18.2)	0.253	14.0	(-15.5,43.5)	0.352
Current 10-20 cig/day	-15.8	(-61.0,29.5)	0.495	37.7	(5.1,70.2)	0.023
Current >20 cig/day	-71.9	(-117.2,-26.5)	0.002	-12.9	(-50.1,24.3)	0.497

* Forced vital capacity , 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 (***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, 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.

Decline in FEV_1 was 2ml (95%CI 0.4-3.6) larger per year in subjects with one childhood disadvantage factor, 3.8ml (1.0-6.6) larger in those with two factors and 2.2ml (-4.8-9.2) larger in those with ≥3 factors; decline increased with an increasing number of childhood disadvantage factors (table 4). For comparison, smoking 10-20 cigarettes daily was associated with 4ml larger lung function decline per year (table 4). When excluding subjects with childhood asthma, the findings were similar (online repository, table 4b). Adjustment for current respiratory symptoms, asthma or atopy did not alter the findings (data not given).

Table 4. Associations of decline in adult FEV_1* with individual childhood disadvantage factors (**A**) and with number of childhood disadvantage factors (**B**) in 5608 persons with complete data.

	adjusted decline in FEV_1 (ΔFEV_1†, ml/year)	**95% CI**	**p-val**
A			
Baseline decline (ml/yr) ‡	*-23.2*		
Maternal asthma	-0.5	(-3.7,2.7)	0.770
Paternal asthma	-2.1	(-5.3,1.0)	0.186
Childhood asthma	-5.9	(-10.7,-1.2)	0.013
Severe respiratory infection < 5 yrs	-1.1	(-3.6,1.4)	0.385
Maternal smoking	-1.3	(-3.2,0.6)	0.175
B			
Baseline decline (ml/yr) ‡	*-23.4*		
Number of childhood factors			
1	-2.0	(-3.6,-0.4)	0.014
2	-3.8	(-6.6,-1.0)	0.009
3 or more	-2.2	(-9.2,4.8)	0.542
p for trend	*0.003*		
For comparison:			
Adult smoking status			
Ex	3.5	(1.8,5.3)	<0.001
Current <10 cig/dia	-0.7	(-3.7,2.3)	0.639
Current 10-20 cig/dia	-4.0	(-6.9,-1.1)	0.006
Current >20 cig/dia	-9.5	(-11.9,-7.0)	<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, change in BMI, mid BMI, sex, the 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, 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.

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

Table 5. Associations of COPD* with individual childhood disadvantage factors (**A**) and with number of childhood disadvantage factors (**B**). Analyses include 8201 measurements in men and 8633 measurements in women with complete data.

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

* COPD defined as FEV_1/FVC ratio <0.70 and FEV_1<80% predicted; based on pre-bronchodilator 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.

DISCUSSION

This analysis of a large multi-centre 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 age 5 years and maternal smoking were associated with 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 increasingly lower level of FEV_1 in adult life, they had 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 slightly smaller impact on lung function decline. These findings were similar for men and women, smokers and non-smokers, never-asthmatics and non-symptomatics, and were consistent across different geographical areas.

To the authors' knowledge, there are no other studies that attempt 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 affects lung function level in early adulthood but not decline in lung function. The lack of association between the individual factors and decline agrees with our study; when we considered each risk factor separately there were only minor effects. However, when attempting to describe overall early life disadvantage by counting number of disadvantage factors 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 associations, thus, the observed estimates may underestimate the true effects. Another problem of this study was lack of information on potentially important factors like childhood exposure to air pollution and childhood nutrition, which may also have contributed to underestimate the true importance of early life disadvantage. Only pre-bronchodilator spirometric measures were available. The findings were consistent when excluding subjects who had ever had diagnosed asthma or currently had respiratory symptoms; however, the findings might relate to asymptomatic bronchoconstriction rather than fixed airway damage; this should be investigated in future studies.

There are several possible mechanisms for how 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, i.e. by causing persistent inflammation[33]. This could possibly explain the persistence of effects of childhood disadvantage in adulthood and larger lung function decline. Both lung growth impairment and persistent inflammation might explain the demonstrated higher risk of COPD

among subjects with childhood disadvantage. Finally, early life factors might possibly increase susceptibility to subsequent risk factors. In our study smoking did not interact with childhood disadvantage, thus increased vulnerability to smoking among subjects with childhood disadvantage was not 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 for 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 lung function level when analysing each childhood disadvantage factor separately. However, the results remained practically unchanged when excluding childhood asthma (figure 2F, online tables 4A-C), and the observed associations with FEV_1, decline in FEV_1 and COPD were independent of current adult asthma (figure 2E, 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, effects of early life factors on adult asthma may possibly 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. Thus environmental and genetic contributions of these factors cannot easily be separated.

In conclusion, this study suggests that adult respiratory health to a large extent originate 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. Programs focusing on maternal smoking in pregnancy and the peri-natal period are likely to be as beneficial as programs 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.

REFERENCES

1. Speizer FE, Tager IB. Epidemiology of chronic mucus hypersecretion and obstructive airways disease. Epidemiol Rev 1979; 1:124-42.
2. Eder W, Ege MJ, von Mutius E. The asthma epidemic. N Engl J Med 2006; 355:2226-35.
3. Svanes C, Jarvis D, Chinn S, Burney P. Childhood environment and adult atopy: results from the European Community Respiratory Health Survey. J Allergy Clin Immunol 1999; 103:415-20.
4. Marossy AE, Strachan DP, Rudnicka AR, Anderson HR. Childhood chest illness and the rate of decline of adult lung function between ages 35 and 45 years. Am J Respir Crit Care Med 2007; 175:355-9.
5. Barker DJ, Godfrey KM, Fall C, Osmond C, Winter PD, Shaheen SO. Relation of birth weight and childhood respiratory infection to adult lung function and death from chronic obstructive airways disease. Bmj 1991; 303:671-5.
6. Shaheen SO, Barker DJ, Holgate ST. Do lower respiratory tract infections in early childhood cause chronic obstructive pulmonary disease? Am J Respir Crit Care Med 1995; 151:1649-51; discussion 1651-2.
7. Merkus PJ, ten Have-Opbroek AA, Quanjer PH. Human lung growth: a review. Pediatr Pulmonol 1996; 21:383-97.
8. Hislop AA, Wigglesworth JS, Desai R. Alveolar development in the human fetus and infant. Early Hum Dev 1986; 13:1-11.
9. Wang X, Dockery DW, Wypij D, et al. Pulmonary function growth velocity in children 6 to 18 years of age. Am Rev Respir Dis 1993; 148:1502-8.
10. Burrows B, Cline MG, Knudson RJ, Taussig LM, Lebowitz MD. A descriptive analysis of the growth and decline of the FVC and FEV1. Chest 1983; 83:717-24.
11. Tager IB, Segal MR, Speizer FE, Weiss ST. The natural history of forced expiratory volumes. Effect of cigarette smoking and respiratory symptoms. Am Rev Respir Dis 1988; 138:837-49.
12. de Marco R, Accordini S, Cerveri I, et al. An international survey of chronic obstructive pulmonary disease in young adults according to GOLD stages. Thorax 2004; 59:120-5.
13. Samet JM, Tager IB, Speizer FE. The relationship between respiratory illness in childhood and chronic air-flow obstruction in adulthood. Am Rev Respir Dis 1983; 127:508-23.
14. Lodrup Carlsen KC, Jaakkola JJ, Nafstad P, Carlsen KH. In utero exposure to cigarette smoking influences lung function at birth. Eur Respir J 1997; 10:1774-9.
15. Stick SM, Burton PR, Gurrin L, Sly PD, LeSouef PN. Effects of maternal smoking during pregnancy and a family history of asthma on respiratory function in newborn infants. Lancet 1996; 348:1060-4.
16. Gilliland FD, Berhane K, McConnell R, et al. Maternal smoking during pregnancy, environmental tobacco smoke exposure and childhood lung function. Thorax 2000; 55:271-6.
17. Cook DG, Strachan DP, Carey IM. Health effects of passive smoking. 9. Parental smoking and spirometric indices in children. Thorax 1998; 53:884-93.
18. Jaakkola MS, Ernst P, Jaakkola JJ, N'Gan'ga L W, Becklake MR. Effect of cigarette smoking on evolution of ventilatory lung function in young adults: an eight year longitudinal study. Thorax 1991; 46:907-13.
19. Upton MN, Watt GC, Davey Smith G, McConnachie A, Hart CL. Permanent effects of maternal smoking on offsprings' lung function. Lancet 1998; 352:453.
20. Svanes C, Omenaas E, Jarvis D, Chinn S, Gulsvik A, Burney P. Parental smoking in childhood and adult obstructive lung disease: results from the European Community Respiratory Health Survey. Thorax 2004; 59.

21. Shaheen SO, Barker DJ, Shiell AW, Crocker FJ, Wield GA, Holgate ST. The relationship between pneumonia in early childhood and impaired lung function in late adult life. Am J Respir Crit Care Med 1994; 149:616-9.
22. Johnston ID, Strachan DP, Anderson HR. Effect of pneumonia and whooping cough in childhood on adult lung function. N Engl J Med 1998; 338:581-7.
23. Dharmage SC, Erbas B, Jarvis D, et al. Do childhood respiratory infections continue to influence adult respiratory morbidity? Eur Respir J 2008.
24. Lawlor DA, Ebrahim S, Davey Smith G. Association of birth weight with adult lung function: findings from the British Women's Heart and Health Study and a meta-analysis. Thorax 2005; 60:851-8.
25. Canoy D, Pekkanen J, Elliott P, et al. Early growth and adult respiratory function in men and women followed from the fetal period to adulthood. Thorax 2007; 62:396-402.
26. Strunk RC, Weiss ST, Yates KP, Tonascia J, Zeiger RS, Szefler SJ. Mild to moderate asthma affects lung growth in children and adolescents. J Allergy Clin Immunol 2006; 118:1040-7.
27. Sears MR, Greene JM, Willan AR, et al. A longitudinal, population-based, cohort study of childhood asthma followed to adulthood. N Engl J Med 2003; 349:1414-22.
28. Phelan PD, Robertson CF, Olinsky A. The Melbourne Asthma Study: 1964-1999. J Allergy Clin Immunol 2002; 109:189-94.
29. Chinn S, Jarvis D, Melotti R, et al. Smoking cessation, lung function, and weight gain: a follow-up study. Lancet 2005; 365:1629-35; discussion 1600-1.
30. Buist AS, McBurnie MA, Vollmer WM, et al. International variation in the prevalence of COPD (the BOLD Study): a population-based prevalence study. Lancet 2007; 370:741-50.
31. Burgess JA, Walters EH, Byrnes GB, Wharton C, Jenkins MA, Abramson MJ, Hopper JL, Dharmage SC. Who remembers whether they had asthma as children? J Asthma. 2006 Dec;43(10):727-30.
32. Svanes CD, S. Sunyer, J. Zock, JP. Norbäck, D. Wjst, M. Heinrich, J. Jarvis, D. de Marco, R. Plana, E. Villani, S. Antó, JM. Long-term reliability in reporting of childhood pets by adults interviewed twice, nine years apart. Results from the European Community Respiratory Health Survey I and II. Indoor Air 2007.
33. Finch CE, Crimmins EM. Inflammatory exposure and historical changes in human life-spans. Science 2004; 305:1736-9.
34. James AL, Palmer LJ, Kicic E, et al. Decline in lung function in the Busselton Health Study: the effects of asthma and cigarette smoking. Am J Respir Crit Care Med 2005; 171:109-14.
35. Lange P, Parner J, Vestbo J, Schnohr P, Jensen G. A 15-year follow-up study of ventilatory function in adults with asthma. N Engl J Med 1998; 339:1194-200.
36. Dijkstra A, Vonk JM, Jongepier H, et al. Lung function decline in asthma: association with inhaled corticosteroids, smoking and sex. Thorax 2006; 61:105-10.

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LEGENDS TO FIGURES

Figure 1. FEV_1 by age according to number of childhood disadvantage factors, in men (A) and women (B) (adjusted for smoking and height); in (C) never-smokers and (D) current smokers (adjusted for sex and height); and in (E) non-symptomatics and (F) never-asthmatics (childhood asthma excluded from childhood disadvantage factors) (adjusted for smoking, sex, and height). The curves were fitted using generalized additive models (GAM), 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 ages 45-56 years.