ORIGINAL ARTICLE

Combined Impact of Smoking and Early-Life Exposures on Adult Lung Function Trajectories

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Abstract

Rationale: Both adverse early-life exposures and adult smoking can negatively influence adult lung function trajectory, but few studies consider how the impact of early-life exposures may be modified by subsequent smoking.

Methods: The Medical Research Council National Survey of Health and Development is a nationally representative cohort, initially of 5,362 individuals, followed since enrollment at birth in March 1946. Using data collected prospectively across life and multilevel modeling, we investigated how the relationships between early-life exposures (infant lower respiratory infection, manual social class, home overcrowding, and pollution exposure) and FEV_1 and FVC trajectories between ages 43 and 60–64 years were influenced by smoking behavior.

Measurements and Main Results: Among 2,172 individuals, there were synergistic interactions of smoking with infant respiratory infection ($P = 0.04$) and early-life home overcrowding ($P = 0.009$), for FEV_1 at 43 years. Within smoker-stratified models, there were FEV_1 deficits among ever-smokers associated with infant lower respiratory infection (−108.2 ml; $P = 0.001$) and home overcrowding (−89.2 ml; $P = 0.002$), which were not evident among never-smokers (−15.9 ml; $P = 0.69$ and −13.7 ml; $P = 0.70$, respectively). FVC modeling, including 1,960 individuals, yielded similar results. FEV_1 decline was greater in smokers ($P < 0.001$), but there was no effect of any early-life exposure on FEV_1 decline. Neither smoking nor early-life exposures were associated with FVC decline.

Conclusions: Besides accelerating adult FEV_1 decline, cigarette smoking also modifies how early-life exposures impact on both midlife FEV_1 and FVC. These findings are consistent with smoking impairing pulmonary development during adolescence or early adulthood, thereby preventing catch-up from earlier acquired deficits.

Keywords: chronic obstructive pulmonary disease; COPD development; infancy; childhood respiratory infections

Lung function, commonly represented by FEV_1 and FVC, peaks during the third decade of life and then declines with age (1). Both the peak values achieved, and subsequent rates of decline, determine adult lung function trajectory, which in turn influences both the development and progression of chronic obstructive pulmonary disease (COPD) (2–5).

Adult lung function trajectories differ between individuals (2–4, 6, 7). By better understanding the origins of this variation we may be able to develop primary prevention strategies. Exposures across the whole life course can impact lung function, the extent of their impact influenced both by their nature and the stage of life during which they act (8). Early life represents a critical developmental period (4, 9) when exposures, such as respiratory infections (4), can impair lung function development. Furthermore, whereas smoking during adulthood is classically associated with the accelerated decline of FEV_1 (7, 10), smoking during adolescence can interfere with the final stages of pulmonary development influencing both FEV_1 and

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At a Glance Commentary

Scientific Knowledge on the Subject: Both low midlife lung function and smoking-induced acceleration of adult FEV_1 function decline can lead to the development of chronic obstructive pulmonary disease (COPD). Current opinion advocates that adverse early-life exposures correspond to lowered midlife FEV_1 because deficits established during early life track into adulthood. However, no lifelong study has reported how smoking across life may modify the impact of early-life exposures on adult lung function.

What This Study Adds to the Field: This study analyzes data collected prospectively across seven decades of life from a nationally representative sample of 2,172 individuals, monitored since their enrollment at birth during one week in March 1946. To our knowledge, this is the first study indicating that personal smoking behavior modifies how adverse early-life exposures, such as infant respiratory infection and early-life home overcrowding, impact on midlife lung function and thereby influence adult lung function trajectory. Smoking can impair pulmonary development during adolescence/early adulthood, and we propose that this may also prevent recovery from early-life deficits. These findings may partly explain the heterogeneity of lung function values among smokers and help identify individuals with greater susceptibility to developing respiratory conditions such as COPD. This study also reveals potential opportunities to avoid the conversion of early-life disadvantage into adult pulmonary function deficits.

FVC (11). Few of these studies, however, consider how smoking may modify the influence of early-life exposures, or vice versa.

The Medical Research Council (MRC) National Survey of Health and Development (NSHD) has monitored a nationally representative sample of individuals for almost 70 years since birth, recording exposures during early life, their subsequent adult smoking behavior, and their adult lung function (12). This offers a unique opportunity to determine (*1*) how the early environment influenced the risk of infant lower respiratory infection and adult smoking, and (*2*) how early-life exposures impacted adult FEV_1 and FVC level and decline between ages 43 and 60–64 years and whether these relationships were modified by smoking.

Methods

Population Studied

The NSHD is a study of 5,362 individuals, representative of all single births to married women during one week in March 1946 within England, Scotland, and Wales (12). Prospective data have been collected regularly from this nationally representative cohort of men and women since birth, with participation rates of generally 80% or higher (13–15). At age 43 years, 3,632 were interviewed at home by research nurses. Loss to follow-up was due to death (7%), emigration (11%), refusal (16%), and failure to trace (5%) (13). Similar visits were made at ages 53 years (14) and 60–64 years (15). At 60–64 years, the participating sample still remained broadly representative of native-born British men and women of the same age (15).

Data

Lung function. Prebronchodilator lung function was measured at 43 (mean, 43.5; SD, 0.2), 53 (mean, 43.5; SD, 0.2), and 60–64 (mean, 63.3; SD, 1.1) years, quality assured by trained nurses using the same Micro Medical Plus turbine electronic spirometers (Micro Medical Ltd., Rochester, Kent, UK). Three maneuvers were recorded in 1989 and two in 1999 and 2006–2011 but otherwise the same protocol, developed before the publication of the current American Thoracic Society/European Respiratory Society guidelines (16), was followed at each visit. The largest of two reproducible readings, defined as within 150 ml of each other, of FEV_1 and FVC was used in analyses.

Early-life exposures. Early-life exposures refer to lower respiratory infection occurrence, home overcrowding, father's social class, and pollution exposure during infancy. When study members were 2 years old, their parents were asked by health visitors: "Has this baby ever had a lower respiratory infection—that is, bronchitis, bronchopneumonia, or pneumonia?" (17). The health visitors also recorded both the number of occupants and rooms within the home. Home overcrowding is defined as more than one person per room (18, 19). Paternal occupational social class (grouped into manual vs. nonmanual) was recorded at age 4 years (or, if missing, at age 11 or 15 yr) (18). Pollution exposure estimates, based on domestic local coal consumption at ages 0 and 2 years, were used to classify early-life pollution exposure as either high or low (20). Maximal disadvantage in early life was defined as having had an infant lower respiratory tract infection, being exposed to a high pollution level, living in an overcrowded home, and having a father with a manual occupation.

Smoking history. The number of cigarettes individuals smoked per day was recorded at 20, 25, 36, 43, 53, and 60–64 years during nurse interviews or via postal questionnaires. In addition, at age 20, prior smoking behavior was recorded (including age of initiation) and at ages 36, 43, 53, and 60–64, individuals were asked whether they had ever previously smoked one or more cigarettes per day for one or more years. "Never-smokers" consistently denied ever regularly smoking throughout the study. Individuals smoking at least one cigarette per day for at least 1 year were considered ever-smokers. For each individual providing smoking data at least at ages 20 and 43 years, we calculated an estimate of pack-years accrued by age 43 years by multiplying the mean number of cigarettes smoked daily across ages 20, 25, 36, and 43 years by 23 (number of intervening years) and then dividing by 20. Self-rolled cigarettes were converted: 1 oz of tobacco = 25 manufactured cigarettes.

Other covariates. Given their known associations with lung function, birth weight (4) (obtained from hospital records within a few weeks of birth) and both height (cm) and weight (kg) (16) (measured at age 43 yr) and sex were prespecified as covariates. Childhood asthma (defined by occurrence of asthma attacks at ages 6, 11, or 15 yr) was considered a potential confounder. Parental smoking during an individual's childhood (at age 53 yr, individuals were asked whether, during their childhood, their parents had smoked) was also considered a potential confounder.

Data Analysis

A total of 2,172 individuals (48% male) provided complete early-life exposure data, sufficient smoking data to calculate

pack-years accrued by 43 years and reproducible FEV_1 data with concurrent smoking data between ages 43 and 60–64 years. Of these, 1,960 individuals also provided reproducible FVC data.

Early-life exposures and risk of infant lower respiratory infection and adult smoking. χ^2 tests and an independent *t* test were used to investigate infant lower respiratory infection association with other early-life exposures and birth weight, respectively. Multivariable logistic regression models were used to investigate whether the relationships of childhood social class, overcrowding, and pollution exposure with infant respiratory infection were independent of each other after also adjusting for sex and birth weight. χ^2 tests were used to assess differences in ever-smoking according to sex and each early-life exposure. χ^2 tests were also used to assess differences in early-life exposures between individuals included versus not included in analyses.

FEV_1 and FVC at age 43 years and decline according to early-life exposures. The relationship of early-life exposure with FEV_1 and FVC at age 43 years and decline to 60–64 years was analyzed, using multilevel models that account for repeated measures on the same individual. Random effects for both intercepts and slope were included, allowing individual intercepts and slopes to vary.

First, FEV_1 change with age from 43 years onward was modeled (model 0). Number of cigarettes smoked daily between ages 43 and 60–64 years was then included as a time-varying covariate influencing both intercept and slope (by adding a smoking-by-age interaction) (model 1). Different trajectories for men and women were then allowed (by adding sex and sex-by-age interaction), and adjustment was made for height and weight at age 43 years, pack-years accrued by 43 years (a continuous variable), and birth weight. Each early-life exposure (infant lower respiratory infection, father's social class, home overcrowding, and pollution exposure) was added one at a time, and allowed to influence both intercept and slope (model 2B). The final adjusted model included all early-life exposures (model 2A). We repeated this approach to investigate how early-life exposures related to FVC at age 43 years and decline to age 60–64 years.

Modification of early-life exposure influence on FEV_1 and FVC trajectories by adult smoking. Within the final adjusted FEV_1 and FVC model we tested for interactions between each early-life exposure and pack-years accrued by 43 years. We then replaced pack-years accrued by age 43 years and the number of cigarettes smoked daily between ages 43 and 60–64 years with an ever-smoking covariate allowed to influence both intercept and slope, again testing for interactions with each early-life exposure. Where there was evidence of effect modification, we stratified the sample by smoking status and subsequently fitted separate models in ever-smokers and never-smokers. To illustrate the differences between smokers and never-smokers, we plotted estimated mean FEV_1 and FVC decline between 43 and 60–64 years for men of average height and weight who in early life were maximally disadvantaged versus those with no early-life disadvantage. We investigated the effect of adjusting these models for childhood asthma. We also investigated the effect of

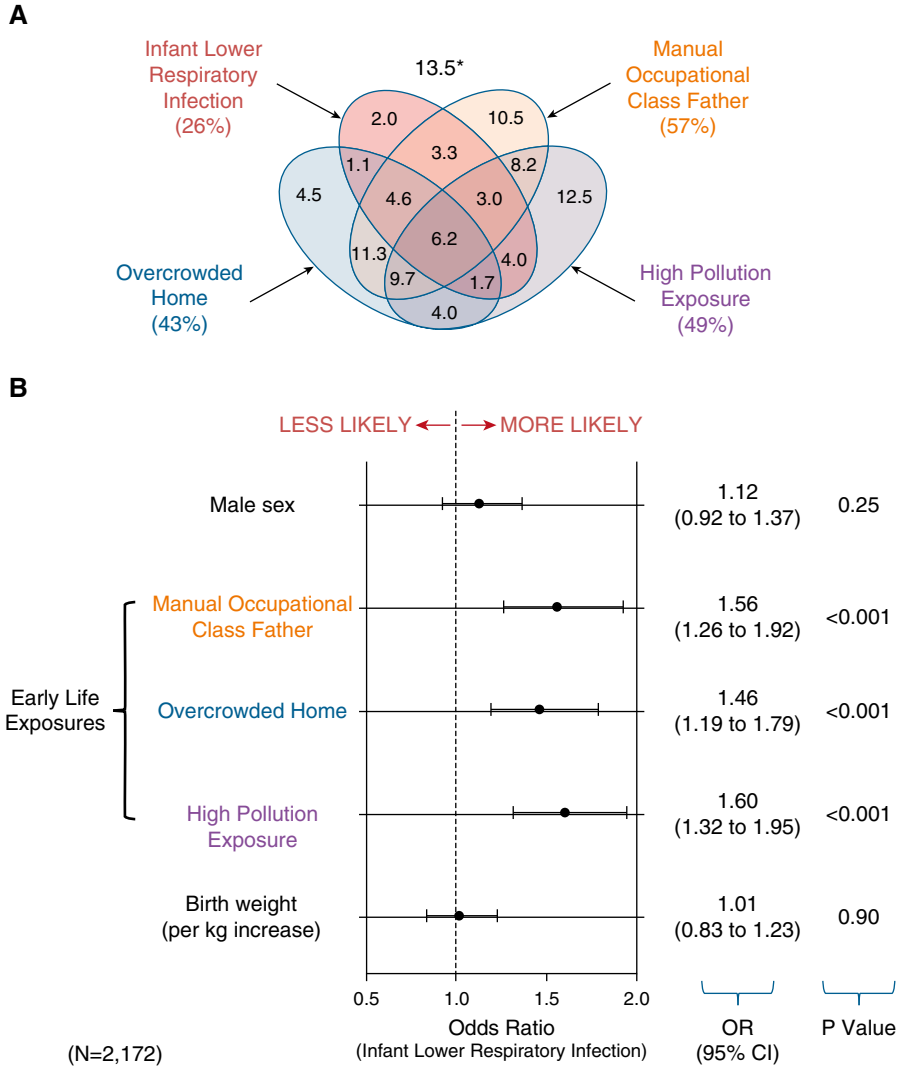

Figure 1. The relationship between infant lower respiratory infection and father's occupational class, home overcrowding, and high pollution exposure during early life among those individuals providing complete data during early life (n = 2,172) within the Medical Research Council National Survey of Health and Development. (*A*) Venn diagram representing the overlapping prevalence (%) of infant lower respiratory infection, father's occupational class, home overcrowding, and high pollution exposure during early life. Numbers shown indicate percentages of the included population (n = 2,172). *Represents those with no lower respiratory infection, father from nonmanual occupational class, no home overcrowding, and low pollution exposure during early life. (*B*) Associations of infant lower respiratory infection, by father's occupational class, home overcrowding, and pollution exposure adjusting for male sex and birth weight. Odds ratios (95% confidence intervals) of having an infant lower respiratory infection according to the presence of each factor were calculated by multiple logistic regression. CI = confidence interval; OR = odds ratio.

adjusting these models for retrospectively reported parental smoking.

To investigate whether data from previous studies support the presence of an interaction between smoking and the infant respiratory infection, regarding adult FEV_1, we sought published studies reporting the adult FEV_1 deficit (in milliliters or liters and with standard deviation reported) associated with prospectively recorded infant respiratory infection from cohorts for which the smoking prevalence was known. We classified these data according to how infant infection had been defined as follows: (*1*) occurrence of pneumonia (severe insult); or (*2*) occurrence of pneumonia, bronchitis, or respiratory tract infection (includes more mild insults). We used metaregression, adjusting for the variance within each study, to test for a relationship between the magnitude of infection-associated FEV_1 deficit and cohort smoking prevalence.

Analyses were performed with SPSS version 22 (IBM Corporation, Armonk, NY) and STATA version 14 (Stata Corporation, College Station, TX).

Results

Early-Life Exposures and Risk of Infant Lower Respiratory Infection and Adult Smoking

Among the 2,172 included in analyses, 26% experienced an infant lower respiratory infection, 57% belonged to manual social class households, 43% lived in overcrowded homes, and 49% were exposed to high pollution, with 6.2% subject to all (maximally disadvantaged) and 13.5% subject to none of these exposures (nondisadvantaged) (Figure 1A). Mean birth weight was 3,398 g (SD, 508 g). Within an adjusted model, infant lower respiratory infections were more likely within manual social class households, overcrowded homes, and with high pollution exposure (Figure 1B; and *see* Table E1 in the online supplement). No association was found with either sex or birth weight.

Of these individuals, 1,299 (60%) had smoked by age 60–64 years, accruing (median) 9.6 (interquartile range [IQR],

Table 1. Estimated Associations between Early-Life Factors and Adult FEV_1 for Subjects between 43 and 60–64 Years of Age*

	FEV_1 Intercept (*ml*) at Age 43 Years			FEV_1 Linear Change per Year (*ml/yr*) between Ages 43 and 60–64 Years		
	Coefficient	**95% CI**	***P* Value**	**Coefficient**	**95% CI**	***P* Value**
Ever-smokers (n = 1,299)						
Constant	−2,305.1	−2,952.8 to −1,657.5	—	−17.3	−29.4 to −5.1	0.001
Male sex	586.3	511.7 to 660.9	<0.001	−1.6	−5.0 to 1.8	0.34
Height at 43 yr (per cm)	31.0	26.8 to 35.3	<0.001	—	—	—
Weight at age 43 yr (per kg)	−2.9	−5.1 to −0.7	0.01	—	—	—
Infant lower respiratory infection, 0–2 yr (yes vs. no)	−108.2	−170.1 to −46.3	0.001	−1.2	−5.2 to 2.7	0.53
Father's occupational class at 4 yr (manual vs. nonmanual)	−71.6	−130.1 to −13.2	0.02	−1.8	−5.3 to 1.8	0.32
Home overcrowding at 2 yr (yes vs. no)	−89.2	−147.0 to −31.5	0.002	1.8	−1.8 to 5.3	0.33
High pollution exposure, 0–2 yr (yes vs. no)	27.0	−27.8 to 81.7	0.33	1.7	−1.7 to 5.1	0.32
Birth weight (per g)	0.07	0.01 to 0.12	0.02	−0.002	−0.005 to 0.002	0.28
Pack-years accrued between ages 20 and 43 yr (per pack-year)	−12.7	−15.4 to −10.0	<0.001	—	—	—
Smoking 43 and 64 yr (per cigarette smoked daily)	2.1	−0.3 to 4.6	0.09	−0.4	−0.6 to −0.2	<0.001
Never-smokers (n = 873)						
Constant	−2,089.8	−2,916.4 to −1,263.2	—	−15.8	−27.4 to −4.3	0.007
Male sex	561.6	468.6 to 654.7	<0.001	1.4	−1.8 to 4.7	0.39
Height at 43 yr (per cm)	28.7	23.4 to 34.1	<0.001	—	—	—
Weight at age 43 yr (per kg)	−1.6	−4.3 to 1.0	0.23	—	—	—
Infant lower respiratory infection, 0–2 yr (yes vs. no)	−15.9	−94.0 to 62.2	0.69	−1.2	−4.9 to 2.6	0.54
Father's occupational class at 4 yr (manual vs. nonmanual)	−39.1	−110.0 to 31.9	0.28	−2.2	−5.6 to 1.1	0.20
Home overcrowding at 2 yr (yes vs. no)	−13.7	−84.3 to 56.8	0.70	2.8	−0.6 to 6.2	0.10
High pollution exposure, 0–2 yr (yes vs. no)	−0.4	−66.4 to 65.7	0.99	−0.7	−3.8 to 2.5	0.69
Birth weight (per g)	0.06	−0.01 to 0.13	0.09	−0.002	−0.005 to 0.001	0.26
Pack-years accrued between ages 20 and 43 yr (per pack-year)	—	—	—	—	—	—
Smoking 43 and 64 yr (per cigarette smoked daily)	—	—	—	—	—	—

Definition of abbreviation: CI = confidence interval.

*Shown are the estimated associations between early-life factors and adult FEV_1 for subjects between the ages of 43 and 60–64 years, from multilevel models including all variables listed in the table (coefficients for linear change are from risk factor-by-age interactions) among ever-smokers (smoked at some point by age 60–64 yr) and never-smokers (never smoked up to age 60–64 yr). In models including only age (*see* Figure E1, model 0), estimated mean FEV_1 at age 43 was 3.02 L, with an overall FEV_1 decline of 24.8 ml/yr (95% CI, 23.6–26.0). *See* also Figures 2 and 3 and Figure E1.

3.1–19.6) pack-years by 43 years. Seventy percent of smokers began smoking before age 20. Those from manual social class backgrounds more commonly became smokers (63%) than their nonmanual counterparts (56%; $P < 0.001$) (Tables E2 and E4). Ever-smoking did not significantly differ according to infant lower respiratory infection, home overcrowding, or pollution exposure. Males more commonly became smokers (66%) than did females (54%; $P < 0.001$). Those from manual social class backgrounds, from overcrowded homes, or exposed to high pollution during early life were less likely to be included in analyses (Table E3).

FEV_1 and FVC at Age 43 Years and Decline according to Early-Life Exposures

In models including only age (Figures E1 and E2, model 0), estimated mean FEV_1 at age 43 years was 3.02 L, and mean FVC was 3.62 L. Overall, FEV_1 declined by 24.8 ml/yr (95% CI, 23.6–26.0) while FVC declined by 21.7 ml/yr (95% CI, 19.8–23.6). In models including number of cigarettes smoked daily between ages 43 and 60–64 years (Figures E1 and E2, model 1), FEV_1 declined by an additional 0.5 ml/yr/cigarette smoked daily (95% CI, 0.3–0.7) ($P < 0.001$); equivalent to an estimated FEV_1 decline of 33.9 ml/yr (95% CI, 30.6–37.2) among those smoking 20 cigarettes per day compared with 23.8 ml/yr (95% CI, 22.5–25.1) among nonsmokers ($P < 0.001$). In contrast, the number of cigarettes smoked per day was not associated with decline in FVC (0.1 ml/yr/cigarette smoked daily; 95% CI, 0.4 to −0.2; $P = 0.39$).

In models including sex, height, and weight at 43 years, birth weight, pack-years accrued by 43 years, and smoking between 43 and 64 years (Figures E1 and E2, model 2), no early-life exposure was associated with decline in FEV_1 or FVC. Within these models, FEV_1 between ages 43 and 64 was lower in those who experienced infant

Table 2. Estimated Associations between Early-Life Factors and Adult FVC Decline Trajectory for Subjects between 43 and 60–64 Years of Age*

	FVC Intercept (*ml*) at Age 43 Years			FVC Linear Change per Year (*ml/yr*) between Ages 43 and 60–64 Years		
	Coefficient	**95% CI**	***P* Value**	**Coefficient**	**95% CI**	***P* Value**
Ever-smokers (n = 1,157)						
Constant	−3,802.6	−4,633.7 to −2,971.5	—	−12.6	−30.2 to 4.9	0.16
Male sex	701.7	601.0 to 802.3	<0.001	1.9	−3.1 to 6.9	0.46
Height at 43 yr (per cm)	45.0	39.5 to 50.4	<0.001	—	—	—
Weight at age 43 yr (per kg)	−7.1	−10.0 to −4.2	<0.001	—	—	—
Infant lower respiratory infection, 0–2 yr (yes vs. no)	−117.3	−204.7 to −29.8	0.009	0.4	−5.4 to 6.2	0.89
Father's occupational class at 4 yr (manual vs. nonmanual)	−80.6	−163.1 to 1.9	0.06	−2.4	−7.6 to 2.8	0.36
Home overcrowding at 2 yr (yes vs. no)	−93.1	−174.6 to −11.5	0.03	2.4	−2.8 to 7.6	0.37
High pollution exposure, 0–2 yr (yes vs. no)	44.4	−32.7 to 121.5	0.26	2.3	−2.6 to 7.3	0.36
Birth weight (per g)	0.08	0.005 to 0.16	0.04	−0.003	−0.008 to 0.002	0.18
Pack-years accrued between ages 20 and 43 yr (per pack-year)	−12.8	−16.2 to −9.4	<0.001	—	—	—
Smoking 43 and 64 yr (per cigarette smoked daily)	0.9	−2.6 to 4.5	0.60	−0.1	−0.4 to 0.1	0.34
Never-smokers (n = 803)						
Constant	−3,583.9	−4,605.5 to −2,562.3	—	−17.7	−37.3 to 1.9	0.08
Male sex	627.4	504.1 to 750.7	<0.001	5.9	0.3 to 11.6	0.04
Height at 43 yr (per cm)	42.3	35.8 to 48.8	<0.001	—	—	—
Weight at age 43 yr (per kg)	−6.0	−9.3 to −2.8	<0.001	—	—	—
Infant lower respiratory infection, 0–2 yr (yes vs. no)	−18.9	−126.1 to 88.2	0.73	2.9	−3.5 to 9.2	0.38
Father's occupational class at 4 yr (manual vs. nonmanual)	−58.4	−155.6 to 38.9	0.24	0.2	−5.5 to 5.9	0.94
Home overcrowding at 2 yr (yes vs. no)	−40.4	−137.0 to 56.2	0.41	−1.4	−7.2 to 4.3	0.63
High pollution exposure, 0–2 yr (yes vs. no)	−0.6	−91.4 to 90.2	0.99	2.2	−3.2 to 7.5	0.43
Birth weight (per g)	0.09	0.001 to 0.19	0.05	−0.002	−0.008 to 0.004	0.48
Pack-years accrued between ages 20 and 43 yr (per pack-year)	—	—	—	—	—	—
Smoking 43 and 64 yr (per cigarette smoked daily)	—	—	—	—	—	—

Definition of abbreviation: CI = confidence interval.

*Shown are the estimated associations between early-life factors and adult FVC decline trajectory between ages 43 and 60–64 years, from multilevel models including all variables listed in the table among ever-smokers (smoked at some point by age 60–64 yr) and never-smokers (never smoked up to age 60–64 yr). In models including only age (Figure E2, model 0), estimated mean FVC at age 43 years was 3.62 L, with an overall FVC decline of 21.7 ml/yr (95% CI, 19.8–23.6). *See* also Figures 2 and 3 and Figure E2.

lower respiratory infection (−74.5 ml; 95% CI, −123.2 to −25.9; $P = 0.003$), home overcrowding (−60.3 ml; 95% CI, −105.1 to −15.5; $P = 0.01$), and manual social class (−55.5 ml; 95% CI, −100.3 to −9.8; $P = 0.02$) (Figure E1, model 2A). At all ages, FVC deficits of similar magnitude were also associated with infant lower respiratory infection (−80.0 ml; 95% CI, −147.7 to −12.2; $P = 0.02$), home overcrowding (−74.8 ml; 95% CI, −137.2 to −12.5; $P = 0.02$), and manual social class (−68.4 ml; 95% CI, −131.3 to −5.5; $P = 0.03$) (Figure E2, model 2A). Early-life pollution exposure was not associated with either FEV_1 or FVC.

Modification of Early-Life Exposure Influence on FEV_1 and FVC Trajectories by Adult Smoking

An interaction was observed between pack-years accrued by age 43 years and both infant lower respiratory infection occurrence ($P = 0.04$) and home overcrowding ($P = 0.009$) for FEV_1, such that these adverse early exposures were more strongly associated with FEV_1 in those with greater pack-year exposure (Figure E1, model 3). A similar interaction between pack-years accrued and infant lower respiratory infection ($P = 0.02$) was observed for FVC, but the interaction was weaker for home overcrowding ($P = 0.16$) (Figure E2, model 3). We observed similar interactions between ever-smoking and both respiratory infection occurrence and home overcrowding regarding FEV_1 ($P = 0.03$ and $P = 0.01$, respectively) and FVC ($P = 0.03$ and $P = 0.35$, respectively). There was no evidence of interaction between smoking and either social class or pollution exposure regarding FEV_1 or FVC level. Tables 1 and 2 show adjusted FEV_1 and FVC models, respectively, for ever- and never-smokers, and Table E4 compares the characteristics of ever- versus never-smokers.

Among ever-smokers, each pack-year accrued by 43 years was associated with an additional FEV_1 decrease of 12.7 ml (95% CI, 10.0–15.4; $P < 0.001$) and a similar FVC decrement of 12.8 ml (95% CI, 9.4–16.2; $P < 0.001$): equivalent to an estimated 292.1- and 294.4-ml lower FEV_1 and FVC, respectively, for those smoking 20 cigarettes per day since age 20 years (23 pack-years) (Tables 1 and 2, top [ever-smokers] and bottom [never-smokers]). Number of cigarettes smoked per day between ages 43 and 60–64 years was associated with accelerated FEV_1 but not FVC decline (Table 1, top and Table 2, top [ever-smokers]).

Among ever-smokers, lower FEV_1 at age 43 years was associated with infant lower respiratory infection occurrence (−108.2 ml; 95% CI, −170.1 to −46.3; $P = 0.001$), early-life manual social class (−71.6 ml; 95% CI, −130.1 to −13.2; $P = 0.02$), and early-life home overcrowding (−89.2 ml; 95% CI, −147.0 to −31.5; $P = 0.002$) (Table 1, top). Given the lack of association between these early-life exposures and FEV_1 decline, there was no evidence that their association with FEV_1 changed with age. There was no evidence of corresponding associations between early-life factors and FEV_1 among the 873 never-smokers, for whom all coefficients were much smaller (Table 1, bottom). Table 2 (top) shows FVC decrements of similar magnitude, which did not change with age, associated with infant lower respiratory infection (−117.3 ml; 95% CI, −204.7 to −29.8; $P = 0.009$) and early-life home

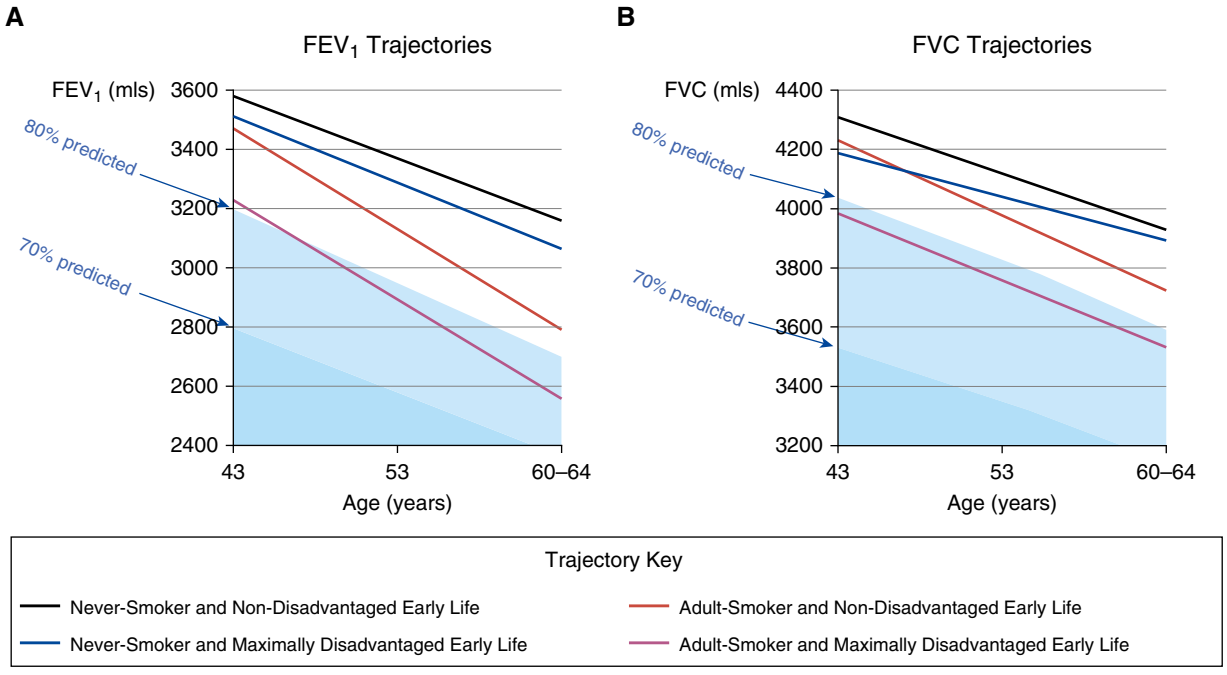

Figure 2. A comparison of the estimated average (*A*) FEV_1 and (*B*) FVC trajectories between ages 43 and 60–64 years for males of average height at age 43 years (175 cm), average weight at age 43 years (78 kg), and average birth weight (3.5 kg) according to adult smoking behavior and early-life disadvantage. Estimated level and slope between 43 and 60–64 years of age was calculated using multilevel models (Tables 1 and 2). Predicted FEV_1 and FVC values according to age were calculated as per Reference 16. Never-smoker = never smoked up to age 60–64 years. Adult smoker = smoked 20 cigarettes per day from age 20 until 60–64 years. Nondisadvantaged early life = no lower respiratory infection, father in nonmanual social class, nonovercrowded home, and low pollution exposure during early life. Maximally disadvantaged early life = lower respiratory infection present, father in manual social class, overcrowded home, and high pollution exposure during early life.

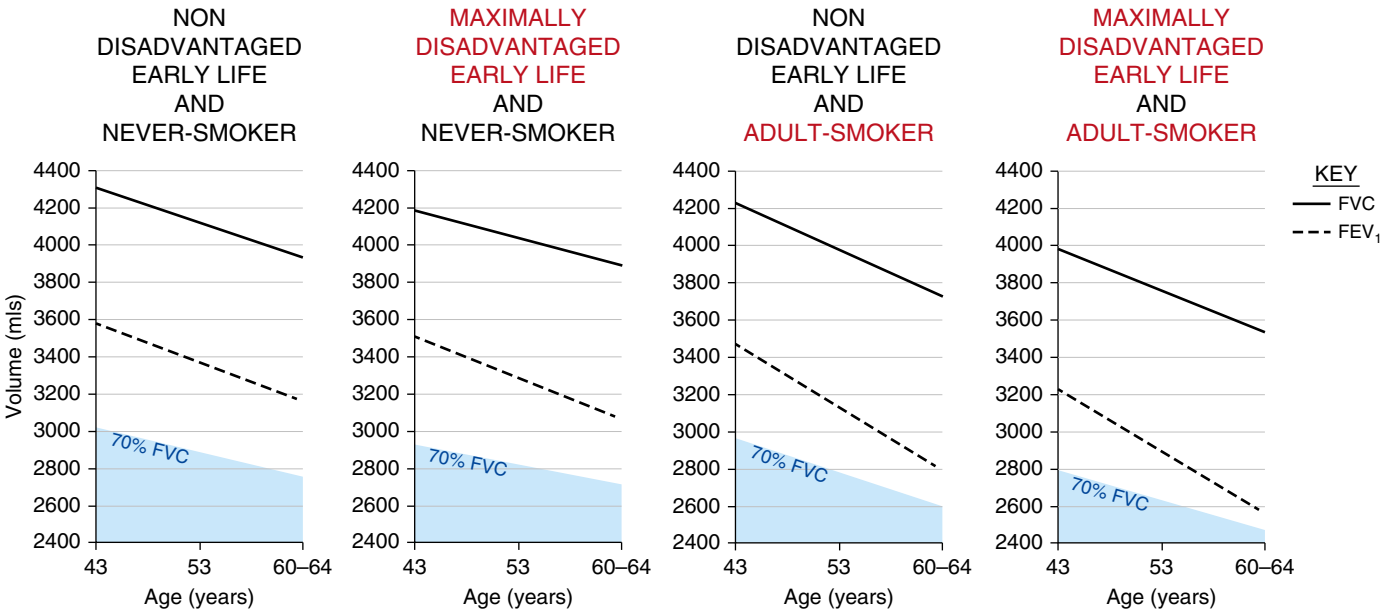

Figure 3. A comparison of the estimated pattern of FEV_1 decline in relation to FVC decline between ages 43 and 60–64 years for males of average height at age 43 years (175 cm), average weight at age 43 years (78 kg), and average birth weight (3.5 kg) according to adult smoking behavior and early-life disadvantage. Estimated level and slope between 43 and 60–64 years of age were calculated using multilevel models (Tables 1 and 2). *Blue-shaded area* indicates zone within which FEV_1 values would meet traditional airflow limitation criteria ($FEV_1/FVC < 0.7$) associated with chronic obstructive pulmonary disease diagnosis. *See* Figure E5 for accompanying FEV_1/FVC plots. Never-smoker = never smoked up to age 60–64 years; adult smoker = smoked 20 cigarettes per day from age 20 until 60–64 years; nondisadvantaged early life = no lower respiratory infection, father in nonmanual social class, nonovercrowded home, and low pollution exposure during early life; maximally disadvantaged early life = lower respiratory infection present, father in manual social class, overcrowded home, and high pollution exposure during early life.

overcrowding (−93.1 ml; 95% CI, −174.6 to −11.5; $P = 0.03$) among ever-smokers. Again, among never-smokers, all early-life exposure coefficients were much smaller and nonsignificant (Table 2, bottom [never-smokers]).

Figure 2 plots estimated FEV_1 and FVC trajectories between 43 and 60–64 years for males (of mean height, weight, and birth weight who were maximally disadvantaged vs. nondisadvantaged [regarding their early-life exposures]). This shows that the difference in mean FEV_1 and FVC between the maximally and nondisadvantaged groups across all ages is considerably greater in smokers than nonsmokers. Corresponding FEV_1 and FVC trajectories from Figure 2 are plotted together in Figure 3 to illustrate how the combined impact of smoking and early-life exposures influences the development of small lung volumes and airflow limitation (the latter characterized by $FEV_1/FVC < 0.70$).

In the models stratified by smoking status, neither adjustment for childhood asthma (Figure E3) nor excluding the 75 individuals (3.5%) reporting asthma during childhood (Figure E4) changed the relationships observed between early-life exposures and smoking with lung function trajectory. The association between childhood asthma and lower FEV_1 was similar among never-smokers (−294.4 ml; 95% CI, −452.4 to −136.3; $P < 0.001$) and ever-smokers (−275.0 ml; 95% CI, −436.8 to −113.1; $P = 0.001$). A similar, but nonsignificant trend was seen for FVC in both smokers and nonsmokers. Appendix E1 also shows that adjustment for parental smoking history did not substantially change our results either.

Figure 4 shows the results of metaregression analysis including data from this and five previous studies (21–25), adjusting for the variance within each study, and suggests that the magnitude of pneumonia-associated deficits increases as cohort smoking prevalence increases ($P = 0.001$). Deficits associated with more mildly defined respiratory infection follow a similar trend. Figure E5 contains details of studies included within this metaregression analysis.

Discussion

This study shows that individuals with adverse exposures during their early lives developed lower FEV_1 and FVC values by age 43 years, but only if they had also become smokers. These deficits were independent of the additional reduction in both FEV_1 and FVC levels accompanying each pack-year already smoked. Subsequently, between ages 43 and 60–64 years, FEV_1 decline was accelerated by smoking, but was not influenced by early-life exposures. Neither smoking nor early-life exposures influenced FVC decline.

Many studies suggest that early-life exposures influence adult respiratory health (6, 26), but the NSHD is the first to prospectively study a nationally representative sample of individuals continuously from birth into their seventh decade, thereby minimizing the recall bias (26) affecting retrospective studies of early life (2, 7, 27–30). Uniquely, the NSHD has documented, during early life, each individual's exposures and then serially recorded smoking behavior across adult life. This allows us to study how the influence of early-life exposures may change and be changed by smoking during adulthood. In contrast to other studies, recruitment after birth within the same week in March 1946 removes the need to adjust for age (7, 31) or symptomatic recruitment bias (7, 32), and together with

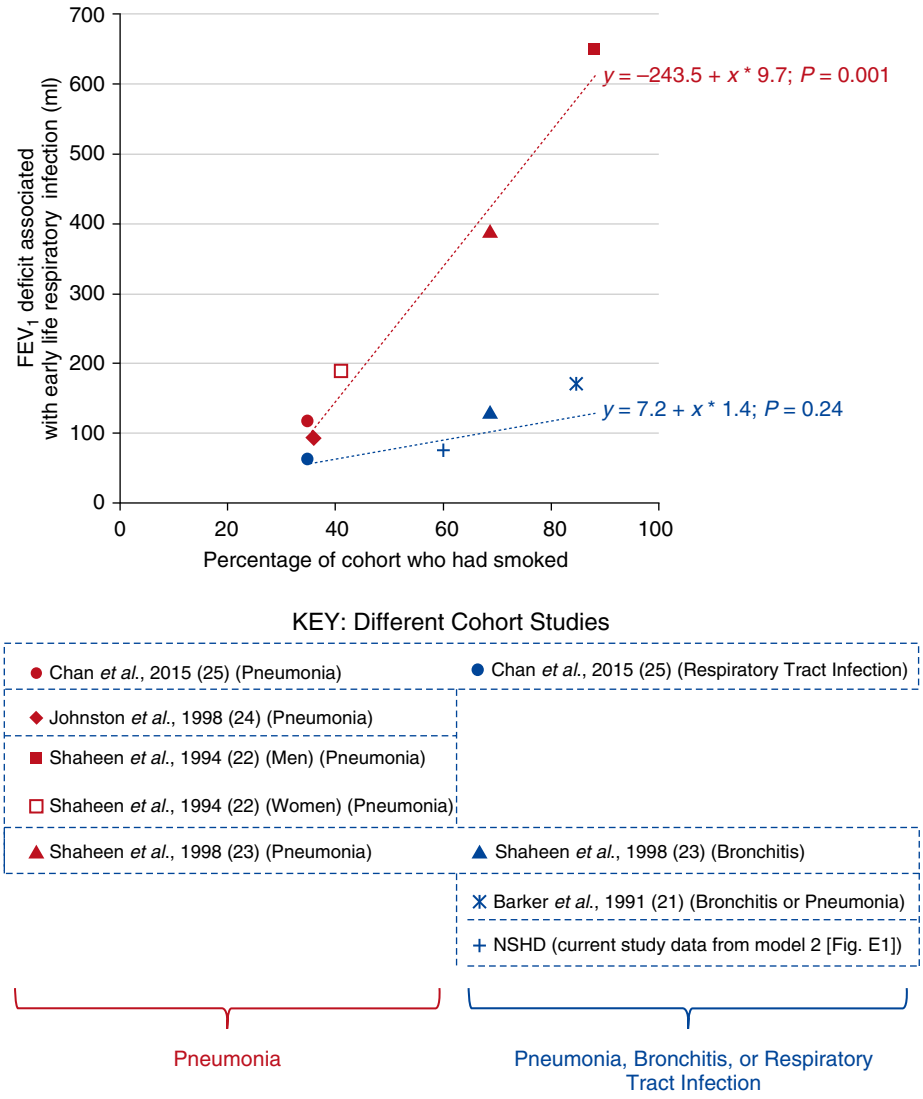

Figure 4. The relationship between the deficit in adult FEV_1 associated with early-life respiratory infection and the prevalence of ever-smoking among study members. The data shown are taken from the National Survey of Health and Development and five other major prospective studies. The graph suggests that the adult FEV_1 deficit associated with infant pneumonia (*red markers*) increases in magnitude as the prevalence of smoking within a study increases. A similar trend is seen across studies reporting the decrement associated with a milder definition of infant respiratory infection (*blue markers*), including "bronchitis" and "respiratory tract infection" rather than just pneumonia. For details of included studies, *see* Figure E5. *Lines* were fitted by metaregression. NSHD = National Survey of Health and Development.

the inclusion of both men and woman (7, 21) from rural and urban areas (32) makes this study more generalizable.

Current opinion advocates that adverse early-life experiences, such as respiratory infections, correspond to diminished midlife FEV_1 because deficits established during early life track into adulthood (6, 33), yet at 43 years of age we found such deficits only among those who had also smoked. A similar interaction between early life, subsequent smoking, and adult respiratory health has been previously reported (29). Furthermore, although most prospective studies simply adjust for smoking (21–24, 33–36), the existence of the interaction between smoking and infant respiratory infection appears consistent with how the adult FEV_1 deficit associated with infant respiratory infection relates to cohort smoking prevalence, as observed across this and five previous major prospective studies (21–25), as shown in Figure 4. Analysis by metaregression, adjusted for the variance within each study, showed that the magnitude of pneumonia-associated deficits increases as cohort smoking prevalence increases ($P = 0.001$). Deficits associated with more mildly defined respiratory infection follow a similar trend. Explaining the basis of this interaction might extend our understanding of both individual smoking susceptibility and the long-term impact of early-life environment.

In agreement with most others, we found no evidence of a relationship between early-life exposures and rate of adult lung function decline (29, 35). In addition, our finding that adverse early-life exposures among smokers were associated with similar decrements in both FEV_1 and FVC at age 43 years is consistent with these individuals having developed smaller-sized lungs. Together, these observations favor an underlying mechanism of impaired development rather than accelerated adult decline (35), which may partly explain the spectrum of FEV_1 values observed among adult smokers with similar FEV_1 decline rates (2).

The lack of evidence of early life–associated pulmonary deficits among never-smokers in midlife also suggests that instead of deficits simply tracking from infancy, smoking modifies how early-life exposures impact on lung development. Within the NSHD, smoking commonly started during adolescence (37), a period when marked FEV_1 and FVC growth (1) is known to permit some recovery from pulmonary function deficits acquired earlier in life (32, 38). However, smoking during this late stage of pulmonary growth impairs both FEV_1 and FVC development (11). Smoking during adolescence may thereby prevent catch-up growth and hence recovery from earlier acquired deficits, perhaps explaining why deficits were apparent only among smokers.

Smoking after age 43 years was associated with accelerated FEV_1, but not FVC decline, theoretically favoring the development of airflow limitation, as illustrated in Figure 3. Although the similar lowering of FEV_1 and FVC at age 43 years we found associated with early-life adversity would not itself result in airflow limitation, the reduced respiratory reserve would predispose to a more severe grade of COPD if airflow limitation were to subsequently develop, as illustrated in Figures 2 and 3.

Although manual social class and home overcrowding, both indicators of lower

income, overlap considerably, their independent associations with later pulmonary deficits suggest that they reflect different inequalities in household resources, behavior or environment (18). Together with high pollution exposure, they also predispose infants to respiratory infections (17, 18), which are historically linked to COPD development (2). Whether this link relates to a common predisposition, such as preexisting small airways, or to the infective event itself, perhaps involving viral sensitization, remains unclear (6, 26). Since the inception of this study seven decades ago, multiple additional perinatal and prenatal determinants of health, such as maternal nutrition, have been identified (4, 39), and these exposures may underpin some of the associations relating to, for example, occupational social class. Confirmation of both the long-term impact of more recently implicated exposures, and the pattern of childhood lung function on adult health, awaits the maturation of subsequent birth cohorts recording both these exposures and lung function across childhood toward peak adult function. However, by showing how smoking may modify the impact of early life, our study identifies a novel perspective from which future investigators may approach such data. In the meantime, our findings provide scope for practical intervention by public health policy makers, especially among adolescent smokers who often believe that cessation at a later stage will still avert significant damage (40).

A major strength of our study is that individuals were monitored from birth into their sixties, but this long study period also presents several limitations. First, the NSHD protocol was designed before guidelines promoting postbronchodilator spirometry measurements, potentially leading to some underestimation of values. Nevertheless, misclassification of postbronchodilator lung function is likely to be random with respect to the exposures of interest (and vice versa), which would be expected to lead to underestimation of effect estimates.

Second, delineating the impact of infant life on adult life necessitates lifelong studies, yet long-running studies inevitably incur losses to follow-up over time. Despite NSHD participation rates generally remaining at 80% or higher throughout the study (12, 41), those with early-life disadvantages were less likely to continue to participate, due to both excess mortality (42) and other attrition. However, our study sample has remained broadly nationally representative (15), suggesting survival to adulthood within the cohort reflects survival among the wider population. Although we cannot rule out the possibility that this might have introduced bias regarding adult spirometry data, we cannot see why the associations under investigation would be different between those who were, and were not, included in the analyses or how this could undermine the applicability of our findings to adult survivors from this generation within the general population.

Finally, the cohort sample is representative of those born in one week in March 1946 in England, Scotland, and Wales whose early-life exposures reflect those of their generation. Today, although living conditions in these countries have improved, poverty and infant respiratory infection remain major issues, particularly across the developing world where smoking prevalence is climbing. In addition, technologies that have improved survival among subsequent generations, for example, after premature birth, may inadvertently lead to the emergence of previously absent adult vulnerabilities with their origins in early life. Furthermore, although smoking prevalence in developed countries is in decline, potential new adult hazards are emerging, for example, electronic cigarette usage. Therefore, the importance of a healthy environment across the life course needs to be championed to prevent unnecessary morbidity.

An important consideration is the complex, potentially reciprocal, relationship between childhood asthma and respiratory infections (22). Childhood asthma prevalence within the NSHD corresponds to other studies of this time (43), as do the size of the asthma-associated adult pulmonary function deficits (44). These deficits occurred irrespective of smoker status, and neither the exclusion of children with asthma nor adjustment for childhood asthma significantly altered our findings. Consequently, childhood asthma appears an unlikely mediator of the interaction detected between smoking and early-life exposures; however, this does not preclude a role for airway hyperactivity or undiagnosed asthma, which will remain key areas of future research.

In summary, this lifelong nationally representative prospective study indicates that besides accelerating adult FEV_1 decline, cigarette smoking also modifies how early-life exposures impact on both midlife FEV_1 and FVC. Our findings are consistent with smoking impairing pulmonary development during adolescence or early adulthood, thereby preventing catch-up from earlier acquired deficits. Although individuals cannot choose their early-life exposures, by choosing not to smoke they may avoid converting early-life disadvantage into adult pulmonary function deficits. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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