

Research Article

# Disadvantaged Early-Life Socioeconomic Circumstances Are Associated With Low Respiratory Function in Older Age

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## Abstract

**Background:** Poor lung function in late life may stem from early-life risk factors, but the epidemiological evidence is inconsistent. We investigated whether individuals who experienced disadvantageous socioeconomic circumstances (SEC) in early life showed lower levels of respiratory function in older age, a steeper decline over time, and whether these relationships were explained by adult-life SEC, body mass index, and physical inactivity in older age.

**Methods:** We used data from the Survey of Health Ageing and Retirement in Europe (2004–2015). Participants' peak expiratory flow (PEF) was assessed with a mini-Wright peak flow meter at second, fourth, and sixth waves. Confounder-adjusted linear mixed-effect models were used to examine the associations between early-life SEC and PEF in older age. A total of 21,734 adults aged 50–96 years (46,264 observations) were included in the analyses.

**Results:** Older adults with disadvantaged early-life SEC showed lower levels of PEF compared with those with advantaged early-life SEC. The association between early-life SEC and late-life PEF persisted after adjusting for adult-life SEC, smoking, physical inactivity, and body mass index. PEF declined with age, but the effect of early-life SEC on this decline was not consistent across robustness and sensitivity analyses.

**Conclusions:** Early life is a sensitive period for respiratory health. Further considering the effect of SEC arising during this period may improve the prevention of chronic respiratory diseases.

**Keywords:** Respiratory system, Peak expiratory flow, Socioeconomic factors, Health status, Aging.

With increasing life expectancy, healthy aging has become a public health challenge (1). Worldwide, 23% of the total global burden of disease is attributable to disorders in adults aged 60 years and older (2). In this population, preventable chronic respiratory diseases, such as chronic obstructive pulmonary disease, are a rising cause of disability and mortality (3). Decreased respiratory function is associated with major adverse effects on the quality of life and disabilities, and is the first step toward pulmonary illness (4). Peak expiratory flow (PEF), the highest measured airflow during forced expiration, is an objective indicator of respiratory function (4,5). Low PEF is a consequence of small lungs, a restrictive lung syndrome, and may reflect chronic obstructive pulmonary disease. Low PEF is also closely associated with adverse health outcomes including disability and mortality (5–7). Because of these associations, a better understanding of the life-course factors underlying the relationship between aging and PEF decline is required.

The origins of poor lung function may stem from early-life risk factors (eg, exposure to pollutants, childhood respiratory infection, and poorly ventilated housing) (8,9) and fetal events resulting in smaller lungs at birth, which are potentially responsible for chronic obstructive pulmonary disease in adulthood (10). Previous studies suggest that disadvantaged early-life socioeconomic circumstances (SEC) are associated with a higher risk of poor respiratory function later in life, but this evidence mainly relies on cross-sectional data (11,12). The emergence of poor lung function in older age is thought to be influenced by the maximum level of respiratory function reached during early adulthood and the rate of decline over aging (13). Longitudinal data allow disentangling the effect of early-life SEC on respiratory function level and rate of decline over aging. Therefore, using this type of data would refine our understanding of the effect of early-life SEC on late-life respiratory health.

Previous longitudinal studies have investigated the associations between early-life SEC and lung function in adulthood (14,15). These studies found no consistent association between early-life SEC and lung function decline. Only one longitudinal study has investigated these associations in older age (16). Results showed that lung function decline was steeper in individuals with disadvantaged early-life SEC (16). However, the study relied on a two-wave design, which is poorly suited for estimating change (17). Particularly, the design cannot shape each individual's growth trajectory and cannot distinguish true change from measurement error. Moreover, it used a unidimensional measure of early-life SEC (ie, father's occupational position), which may have underestimated or overestimated the association between early-life SEC and lung function. Therefore, it is still unclear whether early-life SEC influence later-life lung function's level, its rate of change, or both.

In this study, we sought to determine whether individuals who experienced disadvantageous early-life SEC showed lower levels of PEF in older age and a steeper rate of PEF decline over aging. In addition, we assessed whether these associations were explained by adult-life SEC, smoking behaviors, body mass index (BMI), and physical inactivity in older age.

## Materials and Methods

### Population and Study Design

Data were retrieved from the Survey of Health, Ageing and Retirement in Europe (SHARE) (18), a longitudinal database with

six repeated measurements or waves, every 2 years between 2004 and 2015. PEF was assessed at the second, fourth, and sixth waves. Retrospective life-course data on early-life SEC and main occupational position during adult life were measured in the third wave. Self-reported maximal educational attainment was measured at the first measurement occasion. Household financial situation and covariates (ie, BMI, physical activity, and smoking) were assessed at the first, second, fourth, fifth, and sixth wave. Here, we included data from individuals aged 50–96 years who participated in the third wave and had at least one measure of PEF. SHARE was approved by the relevant research ethics committees in the participating countries and all participants provided written informed consent.

## Measures

### Early-life SEC

Early-life SEC were determined according to the Wahrendorf and Blane measure of childhood circumstances (19). A five-level categorical variable of “most advantaged,” “advantaged,” “middle,” “disadvantaged,” and “most disadvantaged” SEC was computed by combining the information of four binary indicators reflecting specific SEC of participants at the age of 10, which were (i) the occupational position of the household's main breadwinner, (ii) the number of books at home, (iii) a measure of overcrowding, and (iv) the housing quality.

### Covariates and prior confounders

The following variables were included: height, childhood respiratory problems including asthma parental smoking, gender, birth cohort, participant attrition, and country of residence.

### Mediators

*Adult-life SEC* included participants' highest educational attainment, main occupational position during adult life, and satisfaction with household financial situation.

*Health-related mediators* included participants' pack-year smoking, physical inactivity, and BMI.

### Outcome

PEF was measured with a mini-Wright peak flow meter (20). Interviewers applied standardized instructions to ensure that the expiratory task was performed with maximum effort. At the second, fourth, and sixth waves, PEF was measured twice. The maximum value of the two measurements was used as the outcome. See [Supplementary Material 1](#) for more details on these measures.

### Statistical Analysis

Data were analyzed using linear mixed-effect models, which account for the nested structure of the data (eg, multiple observations within a single participant), thereby providing accurate parameter estimates with acceptable Type I error rates (21). The random structure encompassed random intercepts for participants and countries, and random linear slopes of age for participants. These random slopes estimated each participant's linear growth trajectory. Men and women were combined in the analyses because there was no evidence of any interaction between early- or adult-life SEC indicators

and gender. Nevertheless, all models were controlled for gender. Model 1 tested the associations between early-life SEC and PEF in older age, adjusting for prior confounders. Age was centered at the midpoint of the sample's age range (73 years) and was then divided by 10. Thus, the coefficients yielded effects of the overall PEF change over a 10-year interval. Quadratic age was added to account for potential accelerated declines of PEF over aging. Model 1b included an interaction term between early-life SEC and (linear) age to test whether early-life SEC moderated PEF's rate of decline over aging; a significant interaction would indicate that the rate of PEF decline differs across early-life SEC subgroups. In sum, Model 1 examined the influence of early-life SEC on the overall level of PEF in older age and Model 1b assessed the influence of early-life SEC on the rate of decline of PEF over aging. Model 1b also included an interaction term between birth cohort and (linear) age. Education, main occupational position, and satisfaction with household financial situation were added in Model 2, pack-year smoking in Model 3, and physical inactivity and BMI in Model 4. Interaction terms between these variables and age were included in Model 2b, 3b, and 4b to examine whether they influenced the rate of PEF decline over aging. The *p* values for global effect and trend (eg, linear and quadratic) across all the ordered categories (ie, early-life SEC, birth cohort, satisfaction with household income, and BMI) were provided using likelihood ratio tests and polynomial contrasts, respectively (Supplementary Material 3). All models were also tested and presented using an extreme category (eg, most disadvantaged SEC) as a reference.

#### Robustness and sensitivity analyses

We performed two robustness analyses modeling PEF as a dichotomous (low vs high PEF) instead of a continuous variable. The first analysis was based on regression equations including age, sex, and height, as suggested by the European Respiratory Society, and the second analysis was based on the regression equations reported in Supplementary Materials 5–7.

We performed five sensitivity analyses as follows: (i) excluding participants who died during the survey; (ii) excluding participants who dropped out; (iii) excluding participants with at least one of the following chronic conditions: self-reported heart attack, stroke, chronic lung disease, asthma, or cancer; (iv) controlling for unhealthy eating habits (ie, do the participants eat every day a serving of fruits or vegetables on a regular week?) and alcohol consumption (ie, when drinking, do the participants consume more than two drinks?); and (v) adding an interviewer random effect.

## Results

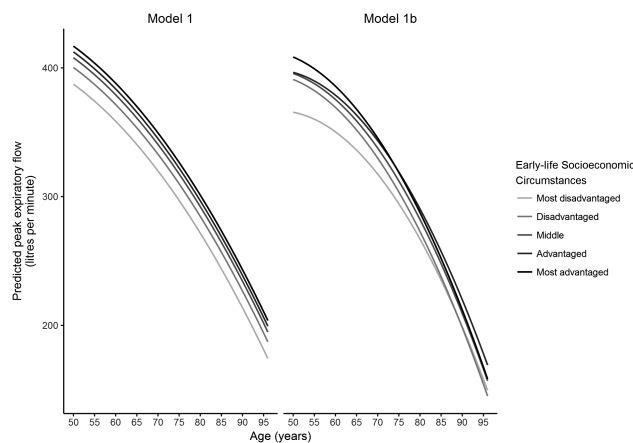
### Descriptive Results

The dataset stratified by early-life SEC is described in Supplementary Material 2. The total sample included 21,734 participants (46,264 observations; 12,431 women) living in 14 European countries, with 1,120 participants (5.6%) in most advantaged, 3,972 (18.3%) advantaged, 5,464 (25.1%) middle, 7,080 (32.6%) disadvantaged, and 3,998 (18.4%) in most disadvantaged early-life SEC.

### Association Between Early-Life SEC and PEF (Model 1 and 1b)

#### Level

The level of PEF was associated with early-life SEC (*p* for global effect <.001). Results showed a gradual decrease of PEF from most advantaged to most disadvantaged early-life SEC. The differences were stronger in the disadvantaged groups (*p* for linear and quadratic trends



**Figure 1.** Predicted peak expiratory flow (PEF) as a function of age and early-life socioeconomic circumstances (SEC). Model 1 did not include interaction terms between early-life SEC and age. Model 1b included interaction terms between early-life SEC and age.

<.001; Supplementary Material 3). For example, the mean difference of predicted PEF level between the two most advantaged groups (ie, most advantaged and advantaged early-life SEC) was 4.44 L/min, whereas the mean difference was 12.95 L/min between the two most disadvantaged groups (ie, most disadvantaged and disadvantaged early-life SEC; Figure 1). In addition, the level of PEF was associated with birth cohort (*p* for global effect <.001), with individuals born between 1929 and 1928 and born after 1945 showing the lowest and highest level of PEF, respectively (Table 1; Supplementary Material 4).

#### Rate of change

The significant linear and quadratic effects of age indicated an accelerated decline of PEF over aging. However, early-life SEC did not influence these linear (*p* = .128) and quadratic trend (*p* = .593). Moreover, overall, the rate of PEF decline was not associated with early-life SEC (*p* for global effect = .135). The rate of PEF decline was associated with birth cohort (*p* for global effect = .020). Results showed that the rate of PEF decline gradually increased from the youngest to the oldest birth cohort (*p* for linear trend = .019), although the variability of this effect was higher in the older cohorts.

### Association Between Adult-Life SEC and PEF (Model 2 and 2b)

#### Level

The associations between early-life SEC and the level of PEF were attenuated but remained significant with the addition of adult-life SEC (Table 1). Lower educational attainment, a disadvantaged occupational position, and lower satisfaction with household financial situation were associated with a decreased level of PEF (Supplementary Material 3). For this latter predictor, the gradual decrease of PEF was steeper in financially satisfied households (*p* for linear and quadratic trends <.001). For example, the mean difference of PEF level between the two most satisfied categories (ie, able to make ends meet “easily” and “fairly easily”) was 13.82 L/min, whereas the mean difference was 1.17 L/min between the two least satisfied categories (ie, able to make ends meet “with some difficulty” and “with great difficulty”).

#### Rate of change

Overall, the rate of PEF decline became significantly associated with early-life SEC (*p* for global effect = .022). However, the linear and quadratic trends in the rate of PEF decline across early-life SEC

**Table 1.** Association of Early-Life Socioeconomic Circumstances (SEC) With the Level and Rate of Decline of Peak Expiratory Flow (PEF) Over Aging

Variables	Model 1		Model 2		Model 3		Model 4	
	<i>b</i> (95% CI)	<i>p</i>	<i>b</i> (95% CI)	<i>p</i>	<i>b</i> (95% CI)	<i>p</i>	<i>b</i> (95% CI)	<i>p</i>
<b>Level</b>								
Birth cohort (ref. born after 1945)								
1939–1945	-5.82 (-10.03 to -1.61)	.007	-5.87 (-10.05 to -1.68)	.006	-6.18 (-10.34 to -2.02)	.004	-5.45 (-9.60 to -1.31)	.010
1929–1938	-15.9 (-21.3 to -10.4)	<.001	-15.0 (-20.44 to -9.56)	<.001	-16.0 (-21.4 to -10.6)	<.001	-13.7 (-19.12 to -8.29)	<.001
1919–1928	-8.89 (-17.93 to 0.14)	.054	-9.09 (-18.09 to -0.08)	.048	-11.3 (-20.70 to -2.76)	.010	-6.28 (-15.27 to 2.71)	.171
<i>p</i> Value for global effect		<.001		<.001		<.001		<.001
<b>Early-life SEC (ref. most disadvantaged)</b>								
Disadvantaged	12.95 (8.53 to 17.38)	<.001	10.65 (6.26 to 15.04)	<.001	11.64 (7.28 to 16.00)	<.001	11.93 (7.58 to 16.27)	<.001
Middle	20.55 (16.02 to 25.08)	<.001	13.70 (9.15 to 18.25)	<.001	14.73 (10.21 to 19.24)	<.001	15.07 (10.57 to 19.56)	<.001
Advantaged	25.09 (19.95 to 30.22)	<.001	13.92 (8.68 to 19.16)	<.001	15.43 (10.22 to 20.63)	<.001	15.92 (10.73 to 21.10)	<.001
Most advantaged	29.53 (22.39 to 36.67)	<.001	11.88 (4.51 to 19.25)	.002	13.28 (5.97 to 20.60)	<.001	14.08 (6.78 to 21.37)	<.001
<i>p</i> Value for global effect		<.001		<.001		<.001		<.001
<b>Rate of change</b>								
Age (10 y follow-up)	-46.32 (-49.38 to -43.25)	<.001	-46.22 (-49.28 to -43.16)	<.001	-46.6 (-49.66 to -43.55)	<.001	-46.1 (-49.11 to -43.01)	<.001
Age (10 y) squared	-4.86 (-6.26 to -3.47)	<.001	-4.66 (-6.05 to -3.27)	<.001	-4.83 (-6.21 to -3.44)	<.001	-4.60 (-5.99 to -3.22)	<.001
<b>Birth cohort (ref. born after 1945)</b>								
1939–1945	11.08 (1.32 to 20.84)	.026	11.45 (1.71 to 21.19)	.021	10.78 (1.05 to 20.51)	.030	11.15 (1.43 to 20.87)	.025
1929–1938	15.18 (-0.54 to 30.89)	.058	15.04 (-0.66 to 30.74)	.060	14.25 (-1.42 to 29.93)	.075	15.10 (-0.57 to 30.77)	.059
1919–1928	17.30 (-7.08 to 41.69)	.164	16.78 (-7.58 to 41.13)	.177	15.82 (-8.51 to 40.14)	.203	16.37 (-7.95 to 40.70)	.187
<i>p</i> Value for global effect		.020		.111		.146		.058
<b>Early-life SEC (ref. most disadvantaged)</b>								
Disadvantaged	-6.51 (-10.79 to -2.22)	.003	-5.76 (-10.04 to -1.48)	.008	-5.68 (-9.94 to -1.43)	.009	-6.06 (-10.31 to -1.82)	.005
Middle	-4.95 (-9.09 to -0.80)	.019	-3.06 (-7.31 to 1.19)	.158	-3.02 (-7.25 to 1.20)	.161	-3.50 (-7.72 to 0.72)	.104
Advantaged	-2.48 (-7.14 to 2.18)	.296	0.63 (-4.27 to 5.53)	.801	0.92 (-3.95 to 5.80)	.711	0.45 (-4.43 to 5.33)	.856
Most advantaged	-7.43 (-14.06 to -0.81)	.028	-2.35 (-9.35 to 4.65)	.511	-1.57 (-8.52 to 5.39)	.659	-2.30 (-9.27 to 4.66)	.517
<i>p</i> Value for global effect		.135		.022		.018		.006

*Notes:* All models were adjusted for gender, height, attrition, childhood respiratory problems, and parental smoking. Model 2 included education, main occupational position, and satisfaction with household financial situation. Model 3 additionally included pack-year smoking. Model 4 additionally included body mass index and physical inactivity. Models 1b–4b included interaction terms of early and adult-life SEC, pack-year smoking, body mass index, and physical inactivity with age to examine whether these predictors influenced the rate of PEF decline over aging. All models included countries as a random level, and random intercepts and random linear slopes of participants' age.

groups remained nonsignificant ( $p = .826$  and  $.384$ , respectively). Education and satisfaction with household financial situation were not associated with the rate of PEF decline. However, a disadvantaged occupational position was associated with a lower rate of decline of PEF.

### Association Between Pack-Year Smoking and PEF (Model 3 and 3b)

#### Level

The associations between early-life SEC and the level of PEF remained significant with the addition of pack-year smoking (Table 1). Higher pack-year smoking was associated with a lower level of PEF ( $p < .001$ ). For example, the mean difference of PEF level between a nonsmoker and a regular smoker (eg, 50 pack-year smoking) was 33.5 L/min.

#### Rate of change

The associations between early-life SEC and the rate of PEF decline remained significant ( $p$  for global effect =  $.018$ ). However, the linear and quadratic trends in the rate of PEF decline across early-life SEC groups remained nonsignificant ( $p = .651$  and  $.304$ , respectively). The rate of PEF decline was greater with higher pack-year smoking ( $p < .048$ ). For example, the mean difference on the linear rate of PEF decline between a nonsmoker and a regular smoker (eg, 50 pack-year smoking) was 3.5 L/min every 10 years.

### Association of Physical Inactivity and BMI With PEF (Model 4 and 4b)

#### Level

The associations between early-life SEC and the level of PEF remained significant after the addition of physical inactivity and BMI (Table 1). Adult-life SEC and pack-year smoking also remained associated with the level of PEF. Physical inactivity and underweight were associated with a lower level of PEF (Supplementary Material 3).

#### Rate of change

The associations between early-life SEC and the rate of PEF decline remained significant ( $p$  for global effect =  $.006$ ) with the addition of physical inactivity and BMI. However, the linear and quadratic trends in the rate of PEF decline across early-life SEC groups remained nonsignificant ( $p$  for linear trend =  $.814$  and  $.283$ , respectively). Disadvantaged occupational position and pack-year smoking remained significantly associated with PEF decline. The rate of PEF decline was not associated with physical inactivity but was marginally greater for participants with obesity (Model 4b).

### Robustness and Sensitivity Analyses

Results of the robustness (ie, dichotomous PEF measure) and sensitivity analyses revealed that the association between early-life SEC and PEF level was robust, but that the effect of early-life SEC on the rate of PEF decline over aging was less consistent (Supplementary Materials 5–9). Excluding participants with chronic conditions yielded results similar to the ones of the main analyses.

## Discussion

### Main Findings

In a European cohort of 21,734 older adults, our results showed a gradual decrease in the level of PEF from most advantaged to most disadvantaged early-life SEC. The association remained significant

after adjusting for adult-life SEC, smoking behaviors, BMI, and physical inactivity. However, even in the fully adjusted model, we did not find a consistent trend in the rate of PEF decline across early-life SEC groups. Overall, these findings suggest that disparities in the level of PEF in older age, but not in the rate of decline over aging, are linked to early-life SEC, independently of socioeconomic and behavioral risk factors during adult life.

### Strengths and Weaknesses

The strengths of our study include a large sample of noninstitutionalized older adults from multiple European countries, a multidimensional measure of early-life SEC, an objective indicator, and a general follow-up of 12 years including three waves with PEF data. These strengths allowed disentangling the level of respiratory function and the rate of decline over aging. However, several limitations should also be noted. First, although PEF is an objective indicator of the respiratory function, it is less consistent and sensitive than the forced expiratory volume in 1 s/forced vital capacity ratio (22). Yet, PEF accurately predicts adverse health outcomes (5–7) and its variability is reduced when performed in accordance with a standardized protocol (22). Second, PEF was measured twice, although three measures are usually recommended (22). Third, early- and adult-life SEC information was obtained from self-reported retrospective data, which may cause recall bias. Nevertheless, recall measures of socioeconomic status showed satisfactory validity. Fourth, participants dropped out or died during the follow-up, which may lead to a potential selection bias in the remaining sample. To address this bias, we adjusted for attrition and conducted sensitivity analyses excluding participants who dropped out or died. These analyses yielded similar results.

### Comparison With Other Studies

Results showed that early-life SEC are associated with the level of PEF in older age. This association persisted in models adjusting for adult-life SEC, smoking behaviors, BMI, and physical inactivity. These findings are in line with the concept of sensitive periods in life-course epidemiology arguing that early-life exposure can affect health in older age (23). A potential explanation for these results is that environmental risk factors—such as exposure to industrial air pollutants in the area of residence—are socially patterned (8,9). For example, living-space insalubrity can lead to repeated upper respiratory tract infections and chronic exposure to dampness, mold, dust, or microparticles, which can lead to long-lasting adverse effects on lung function. Another potential explanation is related to anthropometric factors such as birth weight and height, which are also socially marked. For example, low-socioeconomic status is associated with low birth weight (24), which in turn contributes to a greater risk of death due to chronic obstructive pulmonary disease in relation to a weak lung size and function during adulthood (10). Postnatal growth and puberty are also critical periods of alveolar multiplication (infancy), airway enlargement (childhood), and lungs growth (puberty), all of which contribute to healthy respiratory function during adulthood (25). Disadvantaged early-life SEC may increase chronic social stress resulting from external influences such as family atmosphere, income deficiencies, or exposure to a number of adverse events such as trauma, abuse, neglect, or growing up with a parent with a mental illness or substance abuse (26). In turn, this chronic social stress leads to a greater risk of pulmonary illness (26). Overall, these mechanisms can influence each other and strongly impact postnatal growth and pubertal development, leading to a reduced maximal lung function (13,27).

The influence of early-life SEC on the rate of PEF decline was less consistent. Therefore, our findings suggest that early-life SEC exposure could be more strongly related to the maximum level of attained respiratory function in adulthood than to its rate of decline over aging. This result was not consistent with the longitudinal study examining associations between early-life SEC and decline in lung function in older age (16). However, this study was based on a two-wave design, which is poorly suited to estimating change processes (17), and used a unidimensional measure of early-life SEC (ie, based on father's occupational position), which may have overestimated the associations between early-life SEC and lung function decline.

The level of PEF was lower in individuals with disadvantaged SEC during adulthood (education, household income, and occupational position). A potential explanation of this result relies on the chronic social stress hypothesis (26), as disadvantaged adult-life SEC are associated with a higher level of chronic stress (28) and inflammation (29). Interestingly, inflammation appears to be linked to lung function decline in aging and/or chronic pathology (30). Another potential explanation includes the influence of adult-life SEC on physiological (31) and physical functioning (32–34), which are strongly related to PEF performance. In contrast, the rate of PEF decline was only significantly associated with occupational position, with an accelerated decline observed in individuals with an advantaged occupational position, thereby narrowing the gap over the years between these groups. These findings confirm that SEC risk factors are robustly associated with the level of PEF, whereas their influence on the rate of change seems less clear.

Smoking behaviors, insufficient physical activity, and BMI were independent predictors of a lower level of PEF. This result was expected given the adverse effect of smoking, physical inactivity, and being underweight on physical performance (34,35) and respiratory function (36,37). Although BMI was marginally associated with an accelerated decline of PEF over aging, only smoking behaviors significantly influenced the rate of PEF decline. The influence of smoking and obesity on the decline in PEF was expected (37,38), but not the absence of effect of physical inactivity (39). These results may be explained by the use of self-reported questionnaires to assess physical activity and BMI, which may not accurately reflect participants' physical activity level and BMI, respectively.

## Conclusions

This study suggests that early life is a sensitive period for later-life respiratory health. Socioeconomic life-course trajectories and health-related behaviors in older age do not fully compensate for an unfavorable life start. Results also reveal that the effect of early-life SEC on the level of PEF is more consistent than its effect on the rate of PEF decline over aging. Efforts to prevent chronic respiratory diseases should further consider the key role played by socially patterned events arising early in life.

## Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

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## Contributors

B.C., C.C., S.C., and M.P.B. designed the analyses. B.C. and S.C. analyzed the data. B.C., C.C., and M.P.B. drafted the article. All authors wrote the manuscript.

## Ethical approval

This study was part of the SHARE study, approved by the relevant research ethics committees in the participating countries, and all participants provided written informed consent.

## Data sharing

This SHARE dataset is available at <http://www.share-project.org/data-access.html>.

## Transparency

The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

## Conflict of interest

All authors have completed the ICMJE uniform disclosure form at [www.icmje.org/doi\\_disclosure.pdf](http://www.icmje.org/doi_disclosure.pdf) and declare no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

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