Childhood pneumonia, pleurisy and lung function: a cohort study from the first to sixth decade of life

Jennifer L Perret, Caroline J Lodge, Adrian J Lowe, David P Johns, Bruce R Thompson, Dinh S Bui, Lyle C Gurrin, Melanie C Matheson, Christine F McDonald, Richard Wood-Baker, Cecilie Svanes, Paul S Thomas, Graham G Giles, Anne B Chang, Michael J Abramson, E Haydn Walters, Shyamali C Dharmage on behalf of the TAHS investigators.

SUPPLEMENTARY INFORMATION

Perret JL, *et al. Thorax* 2019; 75:28–37. doi: 10.1136/thoraxjnl-2019-213389

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Methods E1 - Additional lung function testing details

Pre- and post-BD spirometry was performed using the EasyOneTM ultrasonic Spirometer (ndd, Medizintechnik, AG, Switzerland). Participants were asked not to smoke for 4-6 hours prior to testing. Each subject was required to perform at least three pre- and three post-BD trials that met American Thoracic Society (ATS) and European Respiratory Society (ERS) acceptability and repeatability criteria (E1). The highest value for FEV_1 and FVC from acceptable and repeatable trials was recorded. Spirometry was repeated ten minutes after the administration of 200µg of salbutamol via spacer. At age 45, only three participants reported taking an inhaled beta-2-agonist within 4 hours of testing and another three took prednisolone within 24 hours of testing.

Single breath D_LCO was performed according to the ATS/ERS standard (E2). Two technically acceptable T_LCO measurements were obtained which agreed to within 10% or 3 ml CO (STPD)/min/mm Hg of the highest value. D_LCO and D_LCO/VA were neither adjusted to a standard haemoglobin concentration (males 14.6 g/dl; females 13.4 g/dl) nor corrected for the presence of carboxyhaemoglobin. The conversion factor used for T_LCO (ml/min/mmHg) was 2.986 x T_LCO (mmol/min/kPa) (E3).

Lung volume measurements were performed according to the ATS/ERS standard (E4). From the mean of two technically acceptable measurements (agreement within 5%), total lung capacity (TLC) was obtained by adding functional residual capacity (FRC) to the inspiratory capacity (IC), where the latter was measured immediately after FRC without the subject coming off the mouthpiece. Residual volume was obtained from the difference between TLC and vital capacity. Static lung volumes were measured by whole body plethysmography in five of six testing sites, and by multi-breath helium dilution in one (Burnie).

At age 45, all flow volume loops were inspected by an expert physiologist (DPJ) to ensure quality control according to ATS/ ERS acceptability and repeatability criteria. At age 53, around 25% of tests were randomly selected from each tester and reviewed by DPJ.

Methods E2 - Additional clinical definitions

The occupation of the participants' fathers when they were seven-years old was used as a proxy for ***socioeconomic class (1968)***, coded in accordance with the Australian Standard

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Classification of Occupations (ASCO) four-digit codes (E5). For paternal occupation, these codes were then grouped into five major skill groups: i) Managers/ professionals; ii) Associate professionals; iii) Tradespersons and advanced clerical; iv) Intermediate clerical and production; v) Elementary clerical, labourers, and related workers.

Rurality was assigned to the school attended by the participant at the time of the original 1968 survey. Categories included "inner regional Australia", "outer regional Australia", "remote Australia", and "very remote Australia" (E6).

Breast feeding was defined by the response to the 1968 survey question "How was he/she fed in the first three months of life", followed by the options "breast-fed only", "bottle-fed only" and "breast and bottle fed" (E7)?"

Maternal and paternal smoking were defined by an affirmative response of the respective parent or guardian to the 1968 survey question "Do you smoke every day (or six days out of seven)", and if yes, then "How much do you smoke?" followed by three options: "more than 20 cigarettes a day; six to 20 cigarettes a day; less than 6 cigarettes a day".

Childhood current asthma was defined by the presence of asthma and/or wheezy breathing within the preceding 12 months in response to the 1968 survey question, "Has he/she at any time in his/her life suffered from attacks of asthma or of wheezy breathing?" and "How long is it since the last attack?"

Childhood recurrent bronchitis was defined by at least 2 episodes of bronchitis within the preceding 12 months in response to the 1968 survey questions, "Has he/she at any time in his/her life suffered from attacks of bronchitis or attacked of cough with sputum (phlegm) in the chest ("loose" or "rattly" cough)?" and "How long is it since the last attack?"

Adult active asthma (or current asthma) in middle-age was defined by the presence of self-reported asthma or "wheezy breathing" and/or medication use and/or healthcare utilization within the 12 months prior to lung function testing.

Chronic bronchitis was defined by the presence of productive sputum for at least 3 months for 2 consecutive years as determined by multiple survey questions in middle-age

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Methods E3 - Additional statistical methods

While using the repeated measures in middle-age as a single model outcome was an alternative approach to this repeated cross-sectional analytical design, this was not adopted especially as there were smaller numbers who participated in both the 45 and 53 year follow-ups i.e. only 35% of those undergoing lung function testing at age 53 (n=897, see Figure 1 main text).

Raw lung function values (measured in mL or as a ratio) were converted into z-scores using established reference values (spirometry, $T_L$co) and equations (static lung volumes), with lung function expressed as difference from the expected mean, in standard deviation units, based on the individuals age, sex, height and ethnicity. The z-score values for each participant were then used as the outcome in linear regression models. As such, the coefficients represent the associations between exposures and lung function values expressed as z-scores (standard deviation units); i.e. the coefficient represents the change in z-score for each continuous lung function outcome for the exposed category compared with the reference category. Spirometric restriction was defined by FVC < LLN in the absence of airflow obstruction (FEV_1/FVC ≥ LLN), both of which were used as outcomes in logistic regression models.

All analyses were carried out using Stata (release 14, Stata Corporation, Texas, USA). Univariable trends of continuous lung function data were examined across childhood pneumonia/pleurisy categories using the non-parametric trend test across ordered groups, and univariable ordinal logistic regression for categorical outcomes. Multivariable linear/logistic regression were used to examine associations with continuous/categorical lung function outcomes using two different exposure classifications: 1) childhood pneumonia/pleurisy as a binary exposure (ever or never), and 2) a more multi-level exposure consisting of never (0 episodes), infrequent (1–2 episodes) and recurrent (>2 episodes).

Models were adjusted for known confounders of the pneumonia-adult lung function relationship, namely categorical variables of maternal/paternal smoking, socioeconomic status (paternal occupation, rurality of primary school) and history of breast/bottle feeding (E8-9), which were derived directly from pre-specified options of the questionnaire. As the follow-up at age 45 was enriched for asthma and chronic bronchitis by inviting all participants

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with a history of asthma or current bronchitis, these specific models were adjusted for sampling weights. These weights represent the inverse of the probability of being included in the sample, defined by the number in the strata divided by the number selected from each stratum. The observed prevalence of asthma and chronic bronchitis in the enriched sample was reweighted using sampling fractions derived from 1968, 1974 and 2004 surveys.

Childhood lung function measured at the time of the original survey was not included *a priori* given its potential as an intermediary and/or mediator (E10-11). Similarly, temporal relationships between radiologically-confirmed childhood pneumonia and subsequent doctor-diagnosed asthma have been documented (E12-13). Childhood asthma as a mediator was supported by mediation analyses that determined the extent to which that total effect of childhood pneumonia/pleurisy on lung function was mediated by current childhood asthma (E14) by using the medeff command in Stata (E15)(see supplementary Table E4 with text). Therefore, interactions between the effects of childhood pneumonia and current childhood asthma were investigated in part because early childhood asthma had previously been associated with larger lungs in later life (E16), but also to provide estimates without the influence from current childhood asthma (Table E5).

Participant sex, age and height were accounted for by using z-scores (E17-18) with values normalizing differences in estimates between males and females, however, we also tested for biologically plausible sex-related differences (Table E6). To provide estimates in the *absence* of a smoking history, results were also stratified by smoking status (never versus ever-smokers, Table E7). These interaction analyses were performed using childhood pneumonia-pleurisy-ever as a binary variable to maximize statistical power, and stratified results were preferentially reported in the main text if an interaction was identified.

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Table E1: Demographic data for all original survey participants compared with those who underwent spirometry at each follow-up:

Epidemiological data at age 7	Participants of the original survey (N) compared with those with technically acceptable spirometric data at each follow-up (n)			
	At age 7 (N=8,358)	**At age 7 (n=7,097)**	**At age 45 (n=1,329) †‡**	**At age 53 (n=2,600) ‡**
Doctor-diagnosed childhood pneumonia/pleurisy [n (%)] †	*8254 (99)*	*7010 (99)*	*1317 (99)*	*2575 (99)*
Demographics	*8335 (100)*	*7097 (100)*	*1324 (100)*	*2595 (100)*
Age [years (standard deviation)]	6.51 (0.29)	6.51 (0.29)	6.52 (0.29)	6.50 (0.28)
Sex [male]	4270 (51)	3630 (51)	681 (51)	1263 (49)
Rurality of school area [n (%)]	*8224 (98)*	*6997 (99)*	*1309 (98)*	*2570 (99)*
Inner regional Australia	4861 (58)	4195 (59)	838 (63)	1517 (58)
Outer regional Australia	3100 (37)	2590 (36)	438 (33)	982 (38)
Remote Australia	147 (2)	118 (2)	17 (1)	42 (2)
Very remote Australia	116 (1)	94 (1)	16 (1)	29 (1)
Paternal occupation [n (%)]	*7789 (93)*	*6638 (94)*	*1252 (94)*	*2873 (95)*
Managers/ professionals	1625 (19)	1415 (20)	289 (22)	609 (23)
Associated professionals	506 (6)	437 (6)	103 (8)	180 (7)
Tradespersons, advanced clerical	2310 (28)	1978 (28)	377 (28)	743 (29)
Intermediate clerical/ production	2213 (26)	1879 (26)	335 (25)	667 (26)
Elementary clerical, labourers and related workers	1135 (14)	929 (13)	148 (11)	274 (11)
Infant feeding [n (%)]	*8154 (98)*	*6943 (98)*	*1308 (98)*	*2571 (99)*
Breast only	3194 (38)	2741 (39)	549 (41)	1118 (43)
Bottle only	2342 (28)	1947 (27)	335 (25)	650 (25)
Breast and bottle feeding	2618 (31)	2255 (32)	424 (32)	803 (31)
Parental smoking at age 7 [n (%)]				
Maternal smoking	*8045 (96)*	*6852 (97)*	*1297 (98)*	*2547 (98)*
Yes, ≥6 days of 7	3046 (36)	2589 (36)	489 (37)	844 (32)
Paternal smoking	*7851 (94)*	*6679 (94)*	*1270 (96)*	*2504 (96)*
Yes, ≥6 days of 7	4897 (59)	4160 (59)	763 (57)	1457 (56)
Asthma/wheezy breathing [n (%)]	*8358 (100)*	*7097 (100)*	*1329 (100)*	*2600 (100)*
≥1 episode in preceding 12m	902 (11)	749 (11)	308 (23) †	288 (11)
Recurrent bronchitis [n (%)]	*8059 (96)*	*7097 (100)*	*1273 (96)*	*2508 (96)*
≥2 episodes in preceding 12m	2459 (29)	2071 (29)	526 (40) †	811 (32)

Number (percentage) with available data are included in italics

† Follow-up at age 45 was enriched for asthma/chronic bronchitis

‡ Participant with known childhood pneumonia/pleurisy status and lung diffusing capacity measurements: n=1241 (99%) at age 45 and n=2485 (99%) at age 53; static lung volumes at age 45, n=1207 (99%), see table E2

Table E2: Demographic data for original survey participants and those who underwent lung function measurements other than spirometry in middle-age:

Epidemiological data at age 7	Participants of the original survey (N) compared with those with complex lung function tests in middle-age (n)			
	At age 7 (N=8,358)	$T_L$co at age 45 (n=1,253)	Static LV at 45 (n=1,219) †	$T_L$co at age 53 (n=2,510)
Doctor-diagnosed childhood pneumonia/pleurisy [n (%)] †	*8254 (99)*	*1241 (99)*	*1207 (99)*	*2485 (99)*
Demographics	*8335 (100)*	*1248 (100)*	*1214 (100)*	*2505 (100)*
Age [years (standard deviation)]	6.51 (0.29)	6.52 (0.29)	6.51 (0.29)	6.51 (0.28)
Sex [male]	4270 (51)	643 (51)	626 (51)	1216 (48)
Rurality of school area [n (%)]	*8224 (98)*	*1237 (99)*	*1204 (99)*	*2480 (99)*
Inner regional Australia	4861 (58)	805 (64)	788 (64)	1458 (58)
Outer regional Australia	3100 (37)	400 (32)	388 (32)	956 (38)
Remote Australia	147 (2)	18 (1)	15 (1)	37 (1)
Very remote Australia	116 (1)	13 (1)	13 (1)	29 (1)
Paternal occupation [n (%)]	*7789 (93)*	*1183 (94)*	*1151 (94)*	*2388 (95)*
Managers/ professionals	1625 (19)	269 (21)	261 (21)	593 (24)
Associated professionals	506 (6)	101 (8)	97 (8)	174 (7)
Tradespersons, advanced clerical	2310 (28)	361 (29)	350 (29)	715 (28)
Intermediate clerical/ production	2213 (26)	321 (26)	317 (26)	646 (26)
Elementary clerical, labourers and related workers	1135 (14)	131 (10)	126 (10)	260 (10)
Infant feeding [n (%)]	*8154 (98)*	*1234 (98)*	*1200 (98)*	*2482 (99)*
Breast only	3194 (38)	514 (41)	501 (41)	1086 (43)
Bottle only	2342 (28)	316 (25)	307 (25)	621 (25)
Breast and bottle feeding	2618 (31)	404 (32)	392 (32)	775 (31)
Parental smoking at age 7 [n (%)]				
Maternal smoking	*8045 (96)*	*1221 (97)*	*1189 (98)*	*2456 (98)*
Yes, ≥6 days of 7	3046 (36)	459 (37)	446 (37)	795 (32)
Paternal smoking	*7851 (94)*	*1198 (96)*	*1165 (96)*	*2416 (96)*
Yes, ≥6 days of 7	4897 (59)	718 (57)	697 (57)	1404 (56)
Asthma/wheezy breathing [n (%)]	*8358 (100)*	*1253 (100)*	*1219 (100)*	*2510 (100)*
≥1 episode in preceding 12m	902 (11)	308 (25) †	299 (25) †	281 (11)
Recurrent bronchitis [n (%)]	*8059 (96)*	*1199 (96)*	*1167 (96)*	*2423 (97)*
≥2 episodes in preceding 12m	2459 (29)	506 (40) †	491 (40) †	786 (31)

Abbreviations: $T_L$co, transfer factor of the lung for carbon monoxide; LV, lung volumes

Number (percentage) with available data are included in italics

† Follow-up at age 45 was enriched for asthma/chronic bronchitis

Table E3: Differences in childhood pneumonia and spirometry between participants and non-participants

Participants of original survey with pneumonia data (N) with and without technically acceptable spirometric data (n)	Clinical feature when participants were aged 7			
	Doctor-diagnosed pneumonia/pleurisy [n (%)] †	Spirometric function ‡ [z-score measured in SD (SD)]		
		FEV_1	FVC	FEV_1/FVC
At age 7 (N=8,262) †	1177 (14.3)	–0.08 (1.0)	–0.18 (0.9)	+0.19 (1.0)
Spirometric data (n=7,010)	977 (13.9)	–0.08 (1.0)	–0.18 (0.9)	+0.19 (1.0)
Missing data (n=1,252)	200 (16.0)	-	-	-
At age 45				
Spirometric data (n=1,318)	236 (17.9) §	–0.11 (1.0)	–0.15 (1.0)	+0.09 (1.0)
Missing data (n=6,944)	941 (13.6)	–0.07 (1.0)	–0.18 (0.9)	+0.21 (1.0)
At age 53				
Spirometric data (n=2,577)	342 (13.3)	–0.08 (1.0)	–0.18 (0.9)	+0.18 (1.0)
Missing data (n=5,685)	835 (14.7)	–0.07 (1.0)	–0.18 (0.9)	+0.20 (1.0)

Definition for abbreviations: FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; SD, standard deviation

† Pneumonia history available for 8262/8358 = 98.9% participants

‡ Participant numbers were fewer when taking valid childhood spirometry into account: n=1,143/ 5,867 for those with/without spirometry at age 45; n=2,239/ 4,771 for those with/without spirometry at age 53

§ Prevalence 14.4% accounting for sampling weights (see Table 1 main text) as follow-up enriched for asthma and chronic bronchitis

Table E4: Mediation of the pneumonia-pleurisy-lung function relationship by current asthma at age 7

Lung function measure	Mediation analysis effect			
	Indirect effect (%)	Direct effect (%)	Total effect (%)	% of total effect mediated
At age 7				
FEV_1	–7.56	–16.95	–24.52	30.8%
FVC	–0.45	–14.24	–14.69	3.1%
FEV_1/FVC	–12.74	–4.83	–17.57	72.5%
Airflow obstruction†	+3.61	+2.88	+6.49	55.6%
At age 45				
Spirometric restriction‡	+2.01	+7.23	+9.25	21.7%
TLC	–1.12	–31.97	–33.09	3.4%
FRC	+0.05	–11.42	–11.37	4.4%
KCO	+2.60	+58.94	+61.54	4.2%
At age 53				
Spirometric restriction‡	+1.31	+6.65	+7.96	16.5%
KCO	+7.12	+22.85	+29.98	23.7%

Definitions of Abbreviations: BD, bronchodilator; FEV_1,forced expiratory volume in one second; FRC, functional residual capacity; FVC, forced vital capacity; KCO, carbon monoxide coefficient of the lung; TLC, total lung capacity

† Airflow obstruction was defined by FEV_1/FVC ≥ LLN

‡ Spirometric restriction was defined by FVC < LLN in the absence of airflow obstruction (FEV_1/FVC ≥ LLN)

Causal Mediation Analysis was used to determine the extent to which the total 'effect' of childhood pneumonia/pleurisy-ever on selected lung function outcomes was mediated by current childhood asthma. This analysis partitions the **total effect** into an **indirect effect** of childhood pneumonia/pleurisy-ever on childhood/adult lung function (childhood pneumonia/pleurisy-ever acting through current childhood asthma and then current childhood asthma acting on lung function) and a **direct effect** of childhood pneumonia/pleurisy-ever on lung function (that does not act through changes in current childhood asthma induced by childhood pneumonia/pleurisy-ever).

Notably, we observed current childhood asthma to substantially mediate the relationship between childhood pneumonia/pleurisy-ever and obstructed lung function in childhood (% of total effect mediated >50%).

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Table E5: Effect modification of the relationship between childhood pneumonia/pleurisy-ever and lung function by current childhood asthma

Relationship between childhood pneumonia/ pleurisy-ever (≥1 episode) and lung function †		Current asthma at age 7 (N=7,295) ‡			p-interaction
		Regression n ‡	No (n=6,539)	Yes (n=756)	
At age 7					
	FEV_1	5543 / 619	+0.01 (–0.1, +0.1)	+0.07 (–0.1, +0.2)	0.661
	FVC	5543 / 619	+0.02 (–0.1, +0.1)	–0.03 (–0.2, +0.1)	0.436
	FEV_1/FVC	5543 / 619	–0.003 (–0.1, +0.1)	–0.20 (–0.4, –0.02) *	0.036 *
	Airflow obstruction (OR)	5450 / 619	0.83 (0.5, 1.4)	1.63 (0.9, 2.9)	0.105
	Spirometric restriction (OR)	5543 / 601	0.86 (0.6, 1.3)	0.75 (0.4. 1.5)	0.736
At age 45					
	Post-BD FEV_1	919 / 258	+0.02 (–0.2, +0.2)	–0.26 (–0.5, +0.04)	0.109
	Post-BD FVC	919 / 258	–0.12 (–0.3, +0.04)	–0.21 (–0.5, +0.1)	0.534
	Post-BD FEV_1/FVC ratio	919 / 258	+0.27 (+0.1, +0.5) **	–0.04 (–0.3, +0.3)	0.079
	Airflow obstruction (OR)	907 / 253	0.31 (0.1, 0.9) *	1.64 (0.8, 3.5)	0.020 *
	Spirometric restriction (OR)	907 / 208	2.17 (0.8, 5.7)	7.28 (1.9, 28) **	0.213
	D_LCO	855 / 258	+0.24 (+0,02, +0.5) *	–0.09 (–0.4, +0.2)	0.050
	D_LCO/VA	854 / 257	+0.43 (+0.2, +0.7) ***	+0.02 (–0.3, +0.3)	0.026 *
	Alveolar volume	854 / 258	–0.05 (–0.2, +0.2)	–0.24 (–0.5, +0.01)	0.161
	TLC	831 / 251	—0.23 (–0.4, –0.1) **	–0.26 (–0.5, –0.1) *	0.655
	FRC	831 / 251	–0.20 (–0.4, –0.03) *	–0.24 (–0.5, –0.02) *	0.785
	RV	831 / 251	–0.20 (–0.4, –0.03) *	–0.14 (–0.4, +0.1)	0.610
	RV/TLC	822 / 249	–0.07 (–0.2, +0.1)	+0.02 (–0.2, +0.2)	0.300
At age 53					
	Post-BD FEV_1	2101 / 253	–0.09 (–0.2, +0.04)	–0.22 (–0.5, +0.1)	0.368
	Post-BD FVC	2102 / 253	–0.09 (–0.2, +0.03)	–0.11 (–0.4, +0.1)	0.739
	Post-BD FEV_1/FVC ratio	2102 / 253	–0.01 (–0.1, +0.1)	–0.11 (–0.4, +0.2)	0.308
	Airflow obstruction (OR)	2041 / 234	1.00 (0.5, 2.0)	1.71 (0.6, 4.6)	0.542
	Spirometric restriction (OR)	2063 / 225	1.27 (0.5, 3.1)	5.03 (1.03, 24) *	0.204
	D_LCO	2027 / 245	+0.04 (–0.1, +0.2)	+0.13 (–0.2, +0.4)	0.620
	D_LCO/VA	2027 / 245	+0.11 (–0.03, +0.2)	+0.29 (+0.003, +0.6) *	0.367
	Alveolar volume	2027 / 245	–0.07 (–0.2, +0.1)	–0.18 (–0.5, +0.1)	0.566

Definitions of Abbreviations: BD, bronchodilator; FEV_1,forced expiratory volume in one second; FRC, functional residual capacity; FVC, forced vital capacity; OR, odds ratio; RV, residual volume; TLC, total lung capacity; T_Lco, transfer factor of the lung for carbon monoxide

**p<0.05, **p<0.01, ***p<0.001. Analyses with p-interaction values <0.10 have been described in the main text*

† Values are expressed as z-scores (or standard deviations from the mean predicted values for continuous lung function analyses, and odds ratios for categorical lung function analyses; airflow obstruction was defined by FEV_1/FVC < LLN; spirometric restriction was defined by FVC < LLN plus FEV_1/FVC ≥ LLN

‡ Regression numbers relate to complete case analysis within strata of absence/presence of childhood asthma; some variation in logistic models relates to perfect prediction of the childhood asthma analyses with fewer numbers so some confounder categories were excluded

Table E6: Effect modification of the relationship between childhood pneumonia/pleurisy-ever and lung function by sex (male versus female)

Relationship between childhood pneumonia/ pleurisy-ever (≥1 episode) and lung function †		Participant sex (regression N=6,242) ‡			p-interaction
		Regression n ‡	Female (n = 3,049)	Male (n = 3,193)	
At age 7					
	FEV_1	3009 / 3153	–0.003 (–0.1, +0.1)	–0.06 (–0.2, +0.03)	0.460
	FVC	3009 / 3153	+0.02 (–0.1, +0.1)	+0.04 (–0.1, +0.1)	0.852
	FEV_1/FVC	3009 / 3153	–0.02 (–0.1, +0.1)	–0.14 (–0.2, –0.05) **	0.104
	Airflow obstruction (OR)	3009 / 3113	1.34 (0.8, 2.2)	1.28 (0.8, 2.1)	0.892
	Spirometric restriction (OR)	3009 / 3153	1.11 (0.7, 1.8)	0.76 (0.5. 1.3)	0.303
At age 45					
	Post-BD FEV_1	565 / 601	–0.01 (–0.2, +0.2)	–0.14 (–0.4, +0.1)	0.618
	Post-BD FVC	565 / 601	–0.19 (–0.4, +0.02)	–0.15 (–0.4, +0.04)	0.613
	Post-BD FEV_1/FVC ratio	565 / 601	+0.30 (+0.1, +0.5) *	+0.04 (–0.2, +0.3)	0.150
	Airflow obstruction (OR)	550 / 586	0.59 (0.2, 1.6)	0.98 (0.5, 1.9)	0.329
	Spirometric restriction (OR)	511 / 586	7.43 (2.6, 21.5) ***	1.59 (0.6, 4.4)	0.042 *
	D_LCO	533 / 567	+0.15 (–0.1, +0.4)	+0.10 (–0.1, +0.3)	0.771
	D_LCO/VA	532 / 567	+0.27 (–0.01, +0.6)	+0.33 (+0.1, +0.6) **	0.855
	Alveolar volume	532 / 567	–0.10 (–0.3, +0.1)	–0.20 (–0.4, +0.01)	0.667
	TLC	519 / 550	–0.14 (–0.3, +0.01)	–0.29 (–0.5, –0.1) **	0.193
	FRC	516 / 550	–0.16 (–0.3, –0.01) *	–0.17 (–0.3, +0.01)	0.749
	RV	516 / 543	–0.20 (–0.4, –0.03) *	–0.16 (–0.4, +0.04)	0.729
	RV/TLC	516 / 550	–0.11 (–0.3, +0.04)	+0.02 (–0.1, +0.2)	0.141
At age 53					
	Post-BD FEV_1	1207 / 1148	–0.11 (–0.3, +0.1)	–0.19 (–0.4, –0.02) *	0.531
	Post-BD FVC	1207 / 1148	–0.08 (–0.2, +0.1)	–0.12 (–0.3, +0.03)	0.756
	Post-BD FEV_1/FVC ratio	1207 / 1149	–0.06 (–0.2, +0.1)	–0.10 (–0.3, +0.1)	0.766
	Airflow obstruction (OR)	1164 / 1131	1.02 (0.4, 2.5)	1.44 (0.7, 2.8)	0.570
	Spirometric restriction (OR)	1187 / 1128	1.52 (0.4, 5.4)	1.72 (0.8, 3.9)	0.804
	D_LCO	1168 / 1104	+0.14 (–0.02, +0.3)	+0.01 (–0.2, +0.2)	0.280
	D_LCO/VA	1168 / 1104	+0.22 (+0.03, +0.4) *	+0.11 (–0.1, +0.3)	0.405
	Alveolar volume	1168 / 1104	–0.05 (–0.2, +0.1)	–0.11 (–0.3, +0.1)	0.552

Definitions of Abbreviations: BD, bronchodilator; FEV_1,forced expiratory volume in one second; FRC, functional residual capacity; FVC, forced vital capacity; OR, odds ratio; RV, residual volume; TLC, total lung capacity; T_Lco, transfer factor of the lung for carbon monoxide

**p<0.05, **p<0.01, ***p<0.001. Analyses with p-interaction values <0.10 have been described in the main text*

† Values are expressed as z-scores (or standard deviations from the mean predicted values for continuous lung function analyses, and odds ratios for categorical lung function analyses; airflow obstruction was defined by FEV_1/FVC < LLN; spirometric restriction was defined by FVC < LLN plus FEV_1/FVC ≥ LLN

‡ Regression numbers relate to complete case analysis within strata of participant sex; some variation in logistic models relates to perfect prediction of the childhood asthma analyses with fewer numbers so some confounder categories were excluded

Table E7: Effect modification of the relationship between childhood pneumonia/pleurisy-ever and lung function by smoking status (never versus ever)

Relationship between childhood pneumonia and/or pleurisy-ever (≥1 episode) and lung function †		Smoking status (N=1,193 and N=2,772 at ages 45 and 53 respectively) ‡			
		Regression n ‡	Never (n=520 at age 45) (n=1,149 at age 53)	Ever (n=673 at age 45) (n=1,623 at age 53)	p-interaction
At age 7 §					
	FEV_1	6162	–0.03 (–0.1, +0.04)	–	–
	FVC	6162	+0.01 (–0.05, +0.1)	–	–
	FEV_1/FVC	6162	–0.09 (–0.16, –0.02) *	–	–
	Airflow obstruction (OR)	6162	1.31 (0.9, 1.9)	–	–
	Spirometric restriction (OR)	6162	0.92 (0.6, 1.3)	–	–
At age 45					
	Post-BD FEV_1	510 / 655	–0.12 (–0.3, +0.1)	–0.08 (–0.3, +0.15)	0.988
	Post-BD FVC	510 / 655	–0.19 (–0.4, +0.01)	–0.14 (–0.3, +0.06)	0.801
	Post-BD FEV_1/FVC ratio	510 / 655	+0.15 (–0.1, +0.4)	+0.11 (–0.1, +0.3)	0.595
	Airflow obstruction (OR)	500 / 635	0.91 (0.3, 2.5)	0.87 (0.5, 1.7)	0.921
	Spirometric restriction (OR)	365 / 645	7.22 (1.7, 33) **	2.26 (0.97, 5.8)	0.109
	D_LCO	477 / 622	–0.12 (–0.4, +0.1)	+0.27 (+0.02, +0.5) *	0.046 *
	D_LCO/VA	476 / 621	+0.03 (–0.2, +0.3)	+0.41 (+0.15, +0.7) **	0.096
	Alveolar volume	477 / 621	–0.17 (–0.4, +0.1)	–0.05 (–0.3, +0.2)	0.339
	TLC	460 / 608	–0.32 (–0.5, –0.1) ***	–0.15 (–0.3, +0.02)	0.104
	FRC	457 / 602	–0.21 (–0.4, –0.05) *	–0.09 (–0.3, +0.1)	0.146
	RV	456 / 602	–0.24 (–0.4, –0.06) *	–0.08 (–0.3, +0.1)	0.120
	RV/TLC	456 / 602	–0.09 (–0.2, +0.05)	+0.03 (–0.1, +0.2)	0.135
At age 53					
	Post-BD FEV_1	1020 / 1319	–0.17 (–0.3, +0.01)	–0.14 (–0.3, +0.03)	0.919
	Post-BD FVC	1020 / 1319	–0.14 (–0.3, +0.02)	–0.07 (–0.2, +0.07)	0.571
	Post-BD FEV_1/FVC ratio	1021 / 1319	–0.01 (–0.1, +0.1)	–0.11 (–0.3, +0.04)	0.312
	Airflow obstruction (OR)	988 / 1292	2.54 (0.9, 7.3)	1.03 (0.6, 1.9)	0.189
	Spirometric restriction (OR)	1004 / 1295	1.87 (0.7, 5.2)	1.64 (0.7, 4.2)	0.819
	D_LCO	982 / 1279	+0.12 (–0.05, +0.3)	+0.07 (–0.1, +0.2)	0.556
	D_LCO/VA	982 / 1279	+0.26 (+0.1, +0.4) **	+0.11 (–0.1, +0.3)	0.176
	Alveolar volume	982 / 1279	–0.14 (–0.3, +0.04)	–0.03 (–0.2, +0.1)	0.369

Definitions of Abbreviations: BD, bronchodilator; FEV_1,forced expiratory volume in one second; FRC, functional residual capacity; FVC, forced vital capacity; OR, odds ratio; RV, residual volume; TLC, total lung capacity; T_Lco, transfer factor of the lung for carbon monoxide

**p<0.05, **p<0.01, ***p<0.001. Analyses with p-interaction values <0.10 have been described in the main text*

† Values are expressed as z-scores (or standard deviations from the mean predicted values for continuous lung function analyses, and odds ratios for categorical lung function analyses; airflow obstruction was defined by FEV_1/FVC < LLN; spirometric restriction was defined by FVC < LLN plus FEV_1/FVC ≥ LLN

‡ Regression numbers relate to complete case analysis within strata of never/ever smoking; some variation in logistic models relates to perfect prediction of the childhood asthma analyses with fewer numbers so some confounder categories were excluded
§ Results repeated from Tables 3 and 4 in the main text for comparison

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