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# **Mother's Smoking and Complex Lung Function of Offspring in Middle Age: A Cohort Study from Childhood**

Header: *Maternal smoking and adult lung function*

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## ***Summary conflict of interest statements***

Prof McDonald is on Advisory Boards for Novartis, Astra Zeneca and GlaxoSmithKline, has received speaker fees from Astra Zeneca and GlaxoSmithKline, and conference assistance from Boehringer Ingelheim; A/Prof Johns has received an honorarium from GlaxoSmithKline; Prof Abramson has received investigator initiated grants for unrelated research from Pfizer and Boehringer-Ingelheim, a consultancy from AstraZeneca and conference support from Boehringer-Ingelheim and Sanofi; and Prof Thomas has received payment for consultancy (GlaxoSmithKline, Astra Zeneca) and lecturing (GlaxoSmithKline, Novartis). No other authors reported financial disclosures.

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## ***Other***

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Cigarette Smoking/ adverse effects/ epidemiology

Tobacco Smoking/ adverse effects/ epidemiology

### Keywords:

Maternal smoking, airflow obstruction, gas transfer factor, interaction, adult offspring

## ***Abbreviations***

- BD                      bronchodilator
- BMI                     body mass index
- 95% CI                confidence interval, at a levels of 95% certainty
- COPD                 chronic obstructive pulmonary disease
- FEF<sub>25-75%</sub>            forced expiratory flow between 25% and 75% of the FVC
- FEV<sub>1</sub>                  forced expiratory volume in one second
- FVC                    forced vital capacity
- FEV<sub>1</sub>/FVC            the ratio between FEV<sub>1</sub> and FVC
- FRC                    functional residual capacity
- py                      pack-years
- RV                     residual volume
- RV/TLC                the percentage ratio between RV and TLC
- SD                     standard deviation
- SHS                    second-hand tobacco smoke
- TAHS                  Tasmanian Longitudinal Health Study
- TLC                    total lung capacity
- T<sub>L</sub>CO                 carbon monoxide transfer factor of the lung

## ***Summary at a glance***

Heavy maternal smoking during childhood was associated with post-bronchodilator airflow obstruction for middle-aged offspring, and the exposure itself augmented the effects of personal smoking on gas transfer factor. This study suggests that early life exposure might increase an individual's susceptibility for COPD, especially related to personal smoking in later life.

## **ABSTRACT:**

Background and objective: Existing evidence that supports maternal smoking to be a potential risk factor for chronic obstructive pulmonary disease (COPD) for adult offspring has barely been mentioned in major guideline documents, suggesting a need for more robust and consistent data. We aimed to examine whether such early life exposure can predispose to COPD in middle-age, possibly through its interaction with personal smoking.

Methods: The 5<sup>th</sup> decade follow-up of the Tasmanian Longitudinal Health Study (TAHS) cohort which was first studied in 1968 (n=8,583), included a 2004 postal survey (n=5,729 responses) and subsequent laboratory attendance (n=1,389) for comprehensive lung function testing between 2006 and 2008. Multivariable linear and logistic regression models included sampling weights.

Results: Post-bronchodilator airflow obstruction (<5<sup>th</sup> percentile) was detected for 9.3% (n=123) of middle-aged offspring. Its association with heavy maternal smoking (>20 cigarettes/day) during childhood was 2.7-fold higher than for those without exposure (95% confidence interval [1.3, 5.7] p=0.009). Maternal smoking per se approximately doubled the adverse effect of personal smoking on gas transfer factor (z-score -0.46 [-0.6 to -0.3] versus -0.25 [-0.4 to -0.1], p[interaction]=0.048), and was paradoxically associated with reduced residual volumes for non-smokers.

Conclusions: Heavy maternal smoking during childhood appears to predispose to spirometrically-defined COPD. The interplay between maternal and personal smoking on gas transfer factor suggests that early-life exposure increases an individual's susceptibility to adult smoking exposure. These findings provide further evidence to suggest that maternal smoking might be a risk factor for COPD, and reinforce the public health message advocating smoking abstinence.

## INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is now ranked the equal third leading cause of death worldwide,<sup>1</sup> with the mortality rates for low and middle income countries well exceeding those for high income nations.<sup>2</sup> The American Thoracic Society (ATS) document that addressed ‘Novel Risk Factors and the Global Burden of COPD’, reviewed several less traditional risk factors but did not include maternal smoking.<sup>3</sup> Likewise, the only reference cited by the Global Initiative for Obstructive Lung Disease (GOLD) was limited to 18 month old infants.<sup>4</sup> This lack of emphasis on maternal smoking might reflect a relative paucity of data that directly links maternal smoking exposure to low lung function for adult offspring.

The concept that COPD may have origins in early life is now well recognised.<sup>5-7</sup> Maternal smoking adversely affects the ventilatory function of offspring, including neonates,<sup>8</sup> in fants,<sup>9</sup> children<sup>10</sup> and adolescents.<sup>11</sup> The idea that maternal smoking exposure might predispose to COPD in later life appears largely based on these paediatric studies, and of the few adult studies,<sup>12-16</sup> only one examined pre-bronchodilator (BD) spirometry as a categorical outcome.<sup>12</sup> Furthermore, none of these studies looked beyond reductions in ventilatory function to a potential impairment of gas exchange and/or lung mechanics. Further robust and direct evidence in favour of a temporal association between maternal smoking and spirometrically-defined COPD for adult offspring might facilitate its recognition as a predisposing factor.

We aimed to document the relationship between maternal smoking and airflow obstruction, initially when participants were seven-years-old, and again when they were middle-aged. Furthermore, we aimed to investigate the main effects and potential interactions with

personal smoking on complex lung function tests in middle-age, and examine whether the associations varied by sex.

## **MATERIALS and METHODS**

### ***Study Design and Population***

Participants were from the 5<sup>th</sup> decade follow-up of the Tasmanian Longitudinal Health Study (Figure 1), and details that included pulmonary function testing methods have been published.<sup>17-22</sup> Briefly, this population-based cohort born in 1961 (n=8,583) and studied with pre-BD spirometry in 1968 was retraced (n=7,312) and resurveyed (n=5,729 responses) between 2002 and 2005. A subgroup (n=2,373) was selected based on their participation in both the 1968 and 1974 surveys, and was then enriched for asthma and chronic bronchitis, with adequate power to detect the relevant associations. Of those invited, 58.5% (n=1,389) attended the laboratory for a further questionnaire, pre- and post-BD spirometry, skin prick testing, static lung volumes and gas transfer factor measurements, with the same protocols used across testing states. Clinical comparisons between laboratory attendees and non-attendees are presented in Supplementary Table S1.

### ***Data Collection Methods***

Details of the complex lung function testing and conversion to percent of predicted values have been described elsewhere,<sup>17</sup> and summarized in Supplementary Methods S1. For this analysis, the lung function data from the 1968 survey and 5<sup>th</sup> decade laboratory study have been converted to z-scores using reference equations by Quanjer and colleagues<sup>23, 24</sup> and Thompson and colleagues.<sup>25</sup>

## ***Definitions and Statistical Analysis***

***Maternal and paternal smoking in 1968*** were defined by an affirmative response to the 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”. See Supplementary Methods S2 for other clinical definitions.

***Airflow limitation*** was defined by a pre-BD FEV<sub>1</sub>/FVC less than the 5<sup>th</sup> percentile of normal predicted values (z-score < -1.64). ***Post-BD airflow obstruction*** was defined by a ratio of FEV<sub>1</sub>/FVC following 200 µg of salbutamol administered via spacer of less than the 5<sup>th</sup> percentile of normal predicted values.<sup>23</sup> ***Gas trapping*** was defined by a statistically significant increase in the percentage ratio of residual volume (RV) on total lung capacity (TLC), i.e. RV/TLC, compared with the reference participant group.

All analyses were carried out using the statistical software Stata (release 12, Stata Corporation, College Station, Texas, USA), including the population attributable risk function. Sampling weights were the inverse of the probability of being included in the sample, defined as the number in the strata divided by the number of selected from each strata. Logistic and linear regression was used for binary and continuous outcomes respectively. The multivariable models were adjusted for *a priori* confounders including paternal smoking, and additionally adjusted for confounders that changed the estimates of the associations by at least 10% (Supplementary Methods S3). Interactions were investigated based on the biological plausibility of the associations including by sex, and results were

stratified if this was present. In the absence of confounding and effect modification, personal smoking and adult SHS exposure were included as mediators (Supplementary Table S3).

## ***Ethics***

This study was approved by the Human Ethics Review Committees at The Universities of Melbourne (approval number 040375), Tasmania (040375.1) and New South Wales (08094), the Alfred Hospital (1118/04), and Royal Brisbane & Women's Hospital Health Service District (2006/037). Written informed consent was obtained from all participants.

## **RESULTS**

### ***Demographic, Clinical and Lung Function Features***

The clinical characteristics and some lung function data of the 1,389 study participants have been published.<sup>17</sup> Briefly, the mean age [standard deviation (SD)] was 44.9 (0.85) years and 51% were male. Two-thirds (67%, n=925) reported ever having asthma, one-quarter (n=335) had current asthma, and 43% were lifetime non-smokers. Nine percent fulfilled the criteria for post-BD airflow obstruction (n=123, males=69), of whom only 9 participants (<1%) had both post-BD FEV<sub>1</sub>/FVC and T<sub>L</sub>CO levels less than the 5<sup>th</sup> percentile of the normal predicted values.

At baseline in 1968, 38% (n=513) of mothers and 59% (n=756) of fathers were current cigarette smokers, of whom 17% (n=89) of mothers and 34% (n=254) of fathers were heavy smokers of more than 20 cigarettes daily. Twelve percent (n=152) had an estimated combined parental smoking exposure of more than 40 cigarettes daily. Sole maternal

smoking was relatively uncommon (n=107, 8%). The prevalence of parental smoking was similar between the participants and non-participants in the 5<sup>th</sup> decade follow-up laboratory study (Table 1).

The ‘population attributable fraction’ of adult personal smoking that is attributable to maternal smoking was 6.3% in a univariable analysis, compared with 14.5% for paternal smoking (Supplementary Table S3). Additional clinical and lung function characteristics have been summarised in Tables 2 and 3 respectively.

### ***Spirometrically-defined COPD in middle-age***

In a multivariable model, heavy maternal smoking was associated with a 1.8-fold increase in the odds of airflow limitation for seven-year-old children, that was independent of sex and asthma severity (p=0.014) (Table 4). For the sub-group that was studied in middle-age, heavy maternal smoking was associated with a 2.7-fold increase in the odds of having post-BD airflow obstruction (p=0.009), and this was independent of sex and personal smoking status. This estimate was of a similar magnitude to the association for being an ever-smoker [odds ratio (OR) 2.6 (1.6, 4.3), p<0.001]. The association with maternal smoking was apparent for middle-aged males [OR 3.9 (95%CI 1.4, 11), p=0.010] but not females [OR 2.1 (0.7, 6.3), p=0.208], although the sex-difference itself was not significant (p[interaction] >0.70). Results were similar when examined in a sensitivity analysis that excluded those with childhood asthma and/or wheezy breathing [OR 2.6 (0.95, 7.3), p=0.062, n=598]. The estimate for heavy maternal smoking was also similar when the smoking variable included smoking status and pack-years (data not shown).

No associations were found, irrespective of sex, for offspring whose mothers had smoked 20 cigarettes daily or fewer, nor for those with smoking fathers. No interaction was seen between the effects of maternal and personal smoking on mid-life post-BD airflow obstruction for either males or females ( $p[\text{interaction}] > 0.138$ ).

When spirometric values were analysed as a continuous variable, a significant dose response relationship for maternal smoking intensity was seen with regard to childhood airflow limitation (Table 5) though related to an increase in FVC [z-score +0.14 (0.0, 0.2),  $p=0.005$ ]. For middle-aged offspring exposed to heavy maternal smoking, the post-BD FEV<sub>1</sub>/FVC level was around one-third of a standard deviation lower than for those without any exposure ( $p=0.010$ ), approximating an absolute FEV<sub>1</sub>/FVC reduction of 2.9%. This was predominately due to a reduction in post-BD FEV<sub>1</sub> [z-score -0.26 (-0.52 to -0.0),  $p=0.049$ ]. For the sex-stratified analyses, the association remained significant only for males, although again, the sex-interaction was not significant ( $p=0.726$ ) (Supplementary Tables S4). For all participants, there was neither a maternal-personal smoking interaction on post-BD FEV<sub>1</sub>/FVC levels ( $p[\text{interaction}]=0.311$ ), nor an association between maternal smoking and FVC levels ( $p=0.457$ ).

### ***Gas transfer factor in middle-age***

In the multivariable model that used continuous values for T<sub>L</sub>CO as the outcome, for non-smokers, there was no association with maternal smoking when compared with the reference group without either maternal or personal smoking exposure [z-score + 0.1 (-0.2 to +0.2)]. However, maternal smoking significantly augmented the adverse T<sub>L</sub>CO effect of personal smoking [-0.46 (-0.6 to -0.3),  $p<0.001$ ] versus [-0.25 (-0.4 to -0.10),  $p<0.001$ ], and this maternal-personal smoking interaction was modestly significant for all participants ( $p[2\text{-way}$

interaction]=0.048). For male ever-smokers who were exposed to maternal smoking during childhood (Table 6), the z-score of  $-0.49$  ( $-0.7$  to  $-0.3$ ) approximated a reduction of 11.2 ( $-15$  to  $-6.9$ ) percent of predicted, and 1.0 ( $-1.5$  to  $-0.5$ ) mmol/min/kPA. Reduced  $T_LCO$  levels were not associated with paternal smoking.

### ***Lung volumes in middle-age***

For non-smoking offspring, maternal smoking was associated with paradoxical reductions in residual volume [z-score  $-0.29$  ( $-0.5$  to  $-0.1$ ),  $p=0.001$ ] and gas trapping [ $-0.15$  ( $-0.3$  to  $-0.03$ ),  $p=0.011$ ] (Supplementary Table S5). This contrasted the findings for paternal smoking which included elevations in FRC [ $+0.11$  ( $0.01$ ,  $0.2$ ),  $p=0.026$ ], RV [ $+0.16$  ( $0.05$ ,  $+0.3$ ),  $p=0.007$ ], and gas trapping [ $+0.12$  ( $0.04$ ,  $+0.2$ ),  $p=0.002$ ].

## **DISCUSSION**

This is the first population-based study to accurately quantify associations between prospectively recorded information on maternal smoking during childhood and comprehensively documented lung function in middle-age. We estimate the strength of association between heavy maternal smoking and spirometrically-defined COPD for middle-aged offspring to be 2.7-fold higher than for those unexposed, supported by previous data from participants at seven-years of age. We also uncovered a novel interaction by which maternal smoking augmented the adverse effect of personal smoking on gas transfer factor, and found an unexpected association between maternal smoking and reduced lung volumes, suggesting a potential degree of lung restriction.

The link between maternal smoking and reduced airway function for children and adolescent offspring is well-known,<sup>5</sup> , particularly for those with early-onset asthma who had mothers that smoked during pregnancy.<sup>26</sup> A lesser attainment of peak airway function from a reduction in lung growth may contribute to airflow obstruction later in life because the age-related decline tracks along a lower trajectory in adulthood.<sup>5</sup> While maternal smoking from pregnancy has been linked to pre-BD airflow limitation for middle-aged current smokers without current asthma,<sup>12</sup> we confirm an association between heavy childhood exposure and post-BD airflow obstruction for middle-aged offspring, which is independent of asthma and ever-smoking status. Further stratification by sex suggested the possibility of a stronger predisposition for males (Supplementary Tables S4). While a dose-response association was observed for continuous pre-BD FEV<sub>1</sub>/FVC levels when participants were children (Table 5), this was not seen for those tested with post-BD spirometry in middle-age, and this finding is largely unexplained.

Interactions between the effects of parental and personal smoking on airflow obstruction have been suggested by existing data,<sup>12, 14</sup> but T<sub>L</sub>CO and static lung volumes were not part of the study design. We uncovered an interaction between maternal and personal smoking that doubled the loss of T<sub>L</sub>CO for middle-aged ever-smokers, especially for males. Compared with infant girls, boys are predisposed to relatively immature surfactant production, alveolarization and lung maturation by early childhood.<sup>27</sup> Compared with females, male adult smokers with severe COPD have consistently greater emphysematous change as evaluated by lung resection and/or computed tomography scans.<sup>28-30</sup> In this context, we found the early life insult from maternal smoking on gas transfer effectively increased the lung's susceptibility to the later insult of personal smoking for middle-aged offspring. This finding adds another important public health message to the widespread non-smoking

message that already targets the whole population in Western countries. For adolescent sons and daughters of smoking mothers, the decision to abstain from smoking would not only avoid the active smoking effect on their lungs' gas transfer ability, but would also eliminate the contribution from the maternal-personal smoking interaction itself.

The paradoxical reductions in RV and RV/TLC might relate to maternal smoking during pregnancy, which has been linked to chronic foetal hypoxia, low birth weight,<sup>31</sup> altered lung development,<sup>6, 8</sup> and the potential for reduced lung function.<sup>12</sup> However, we acknowledge that our maternal smoking variable may not have been a valid proxy for intrauterine exposure.

Our study has several strengths. It has detailed prospective documentation of parental smoking intensity and of asthma severity when participants were seven-years-old, which minimises recall bias.<sup>17</sup> We used post-BD spirometry which is key to the diagnosis of COPD.<sup>4</sup> Our population-based study included relatively large numbers of individuals both with and without parental and personal smoke exposures, allowing us to examine their interactions. We expressed spirometry values as z-scores after taking the age-related residual standard deviation into account,<sup>23</sup> which, in contrast to absolute<sup>12, 14-16</sup> and percent of predicted values, are not subject to the anthropometric-related biases of age, height, sex and ethnic group.<sup>32</sup>

Our study also has some limitations. The measurement of maternal smoking at a single time-point when participants were seven-years-old does not allow us to determine whether the early life effect occurred *in utero*, in early childhood or both. Without a cumulative measure of maternal smoking exposure, and the lack of data on air pollution and nutrition in

childhood, it is possible that some of the associations might have been influenced by a degree of residual confounding. Mothers who smoked less than six days a week would have classified themselves as “non-current smokers”, the resultant random misclassification may have attenuated or eliminated some true associations, trends or interactions. Although a sampling weight variable was adopted to adjust the regression analyses for the enrichment of our study sample, it remains possible that the selection bias was not entirely eliminated and/or preferentially decreased the participant numbers who had mothers who smoked heavily.<sup>33</sup> The participants were almost exclusively of European ethnicity, which may limit the generalizability to other populations. Similar to the previously mentioned study,<sup>12</sup> our primary outcome of spirometrically-defined COPD might not relate directly to the COPD phenotype that usually manifests clinically beyond mid-adult life.

## **SUMMARY**

As almost 40% of children have at least one parent who smokes worldwide,<sup>34</sup> clarifying the long term lung function consequences of maternal smoking exposure is now crucial. The premise that maternal smoking reduces lung function in adult offspring has been based largely on the appropriate time sequence and biological plausibility, with our study now demonstrating a dose-response association for children. We provide a sound population-based estimate of the strength of the COPD association with maternal smoking for middle-aged offspring, and found maternal smoking to almost double the reduction of gas transfer factor related to personal smoking. While it’s potential as a COPD risk factor for adult offspring has not been comprehensively documented,<sup>3,4</sup> our study suggests that the early life exposure to maternal smoking may increase an individual’s susceptibility to the harms of personal smoking in later life. Identifying those most at-risk might provide an opportunity for a more individualised approach to the prevention of COPD.

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Figure legend

FIGURE 1. TAHS FLOW DIAGRAM 1968-2008

**TABLE 1. PARENTAL CIGARETTE SMOKING INTENSITY**

		1968 Initial survey (n = 8,583)	2006-2008 Lab study (n = 1,389)
Maternal smoking [n(%)]			
	<i>N</i>	8,007 (93)	1358 (98)
	Non-current smokers	4,999 (62)	845 (62)
	Current smoker, at least 6 days/week		
	≤ 5 cigs/day	473 (6)	88 (6)
	6–20 cigs/day	2,016 (25)	336 (25)
	>20 cigs/day	519 (6)	89 (7)
Paternal smoking [n(%)]			
	<i>N</i>	7,626 (89)	1290 (93)
	Non-current smokers	2,954 (39)	534 (41)
	Current smoker, at least 6 days/week		
	≤ 5 cigs/day	280 (4)	50 (4)
	6–20 cigs/day	2,780 (36)	452 (35)
	>20 cigs/day	1,612 (21)	254 (20)
<i>Definition of abbreviation: cigs/day, cigarettes per day</i>			

**TABLE 2. SMOKING AND OTHER CHARACTERISTICS, BY SEX †**

		Laboratory study 2006-2008 (n = 1,389)	
		Males (n = 709)	Females (n = 680)
<i>In childhood, at age 7</i>			
<b>Maternal smoking [n(%)]</b>			
	<i>N</i>	<i>695 (98)</i>	<i>663 (98)</i>
	Non-current smokers	438 (63)	407 (61)
	Current smoker, at least 6 days/week	257 (36)	256 (38)
<b>Paternal smoking [n(%)]</b>			
	<i>N</i>	<i>665 (94)</i>	<i>625 (92)</i>
	Non-current smokers	228 (43)	246 (39)
	Current smoker, at least 6 days/week	377 (57)	379 (61)
Both parents, current smokers (any cigs/day)		189 (28)	199 (31)
Childhood asthma or wheezy breathing [n(%)]		297 (42)	228 (34)
Recurrent childhood bronchitis [n(%)§]		142 (20)	110 (16)
Allergy history [n(%) ‡]		278 (40)	262 (39)
Parental asthma, allergy and/or bronchitis [n(%)]		353 (51)	340 (52)
<i>In middle-age,</i>			
<b>Daily SHS exposure</b>			
	<i>N</i>	<i>699 (99)</i>	<i>670 (99)</i>
	None	504 (72)	520 (78)
	1 – 3 hours daily	124 (18)	95 (14)
	≥ 4 hours daily	71 (10)	55 (8)
<b>Personal smoking</b>			
	<i>N</i>	<i>709 (100)</i>	<i>680 (100)</i>
	Never (n(%))	302 (43)	285 (42)
	Past (n(%))	199 (28)	219 (32)
	Median py [IQR]	9.3 [2, 19]	5.5 [1.8, 14]
	≥ 10 py (n(%))	96 (14)	75 (11)
	Current (n(%))	208 (29)	178 (26)
	Median py [IQR]	25 [14, 35]	18 [9, 26]
	≥ 10 py (n(%))	166 (23)	124 (18)
<b>BMI ≥ 30 kg/m<sup>2</sup>, [n(%)]</b>		214 (30)	210 (31)
<p><i>Definitions of Abbreviations: BMI, body mass index; cigs/day, cigarettes per day; IQR, interquartile range; py, pack-years; SD, standard deviation; SHS, second-hand smoke.</i></p> <p>Number of participants are in italics</p> <p>Of the 1,389 laboratory participants, technically acceptable post-BD spirometry at age 45 was obtained in 1,330 (96%), with complete</p>			

clinical data in 1,374 (99%) with regard to adult SHS exposure at age 45, 1,362 (98%) for lifetime personal smoking, 1,389 (100%) for childhood asthma severity, 1,358 (98%) for maternal smoking and 1,290 (93%) for paternal smoking.

† Further clinical information is detailed in reference <sup>17</sup> and Table S 1

‡ Childhood allergy history includes reported eczema, food allergy and hives at age 7

§ Present if there was a history of bronchitis or "loose/ rattly coughing attacks" at least every 3 months over the last 2 years

**TABLE 3. LUNG FUNCTION MEASURES ‡**

		Laboratory study 2006-2008 (n = 1,389)			
		Males (n = 709)		Females (n = 680)	
Lung function†		Raw Value	Z-score	Raw Value	Z-score
Pre-BD spirometry at age 7 (1968)					
	FEV <sub>1</sub> , L	1.36 (0.22)	- 0.1 (1.0)	1.30 (0.20)	- 0.1 (1.0)
	FEF <sub>25-75%</sub> , L/s	1.8 (0.5)	0.2 (1.0)	1.8 (0.5)	0.2 (1.0)
	FEV <sub>1</sub> /FVC	0.90 (0.1)	0.1 (1.0)	0.91 (0.1)	0.1 (1.0)
Post-BD spirometry, at age 45					
	FEV <sub>1</sub> , L	3.9 (0.6)	- 0.2 (1.0)	2.9 (0.5)	- 0.1 (1.1)
	FEV <sub>25-75%</sub> , L/s	3.6 (1.1)	- 0.2 (1.0)	2.9 (0.9)	- 0.2 (1.1)
	FEV <sub>1</sub> /FVC	0.78 (0.07)	- 0.3 (1.0)	0.79 (0.07)	- 0.2 (1.0)
Single breath T <sub>L</sub> CO, at age 45 §					
	mmol/min/kPa	10.4 (1.8)	0.2 (0.8)	7.9 (1.5)	0.1 (0.9)
Lung volumes, at age 45					
	Total lung capacity, L	7.3 (1.1)	0.3 (0.9)	5.5 (0.8)	0.5 (0.6)
	Residual volume, L	2.1 (0.7)	0.0 (1.0)	1.8 (0.5)	0.1 (0.7)
	RV/TLC, %	28 (6.9)	- 0.4 (0.6)	31 (7.2)	- 0.3 (0.6)
	Functional residual capacity, L	3.4 (0.9)	0.0 (0.9)	2.8 (0.6)	0.1 (0.7)
<p><i>Definitions of Abbreviations:</i> BD, bronchodilator; FEF<sub>25-75%</sub>, forced expiratory flow between 25% and 75% of the forced vital capacity; T<sub>L</sub>CO, transfer factor of the lung for carbon monoxide; RV, residual volume; RV/TLC, percentage ratio between RV and TLC; TLC, total lung capacity.</p> <p>A <i>z-score</i> describes deviation from the mean predicted value, and has a mean of 0 and a standard deviation of 1 in the reference population. Values are expressed as the mean (standard deviation) unless otherwise specified.</p> <p>† Male/female participant numbers were 609/598 for spirometry at age 7 years; 685/645 for post-BD spirometry at age 45 years, where 32 (2.3%) did not meet acceptability and repeatability criteria; 569/556 for T<sub>L</sub>CO at age 45 years; and 627/593 for static lung volumes at age 45 years.</p> <p>‡ Percent of predicted values for spirometry, T<sub>L</sub>CO, TLC, RV and RV/TLC are included in reference <sup>17</sup></p> <p>§ Values were adjusted to a standard haemoglobin concentration and corrected for the presence of carboxyhaemoglobin.</p>					

**TABLE 4: MULTIVARIABLE ASSOCIATIONS WITH AIRFLOW OBSTRUCTION IN CHILDHOOD AND MIDDLE-AGE**

Parental smoking intensity when participants were aged 7	Ratio of FEV <sub>1</sub> /FVC less than the 5 <sup>th</sup> percentile of predicted normal values $\Delta$			
	Childhood pre-BD airflow limitation (aged 7) ‡		Mid-life post-BD airflow obstruction (aged 45) §	
	N = 6,119	Odds ratio (95%CI)	N = 972	Odds ratio (95%CI)
<b>Maternal</b>				
Non-current smoker †	3,852	Ref	619	Ref
Light current (< 6 cigs/day)	355	1.21 (0.7, 2.1)	64	1.77 (0.8, 4.2)
Moderate current (6–20 cigs/day)	1,536	1.15 (0.8, 1.6)	226	0.86 (0.5, 1.6)
Heavy current (> 20 cigs/day)	376	1.79 (1.1, 2.9) *	63	2.71 (1.3, 5.7) **
<b>Paternal</b>				
Non-current smoker †	2,391	Ref	405	Ref
Light current (< 6 cigs/day)	225	1.40 (0.7, 2.7)	43	0.42 (0.1, 2.1)
Moderate current (6–20 cigs/day)	2,246	1.11 (0.8, 1.5)	339	0.85 (0.5, 1.5)
Heavy current (> 20 cigs/day)	1,257	1.13 (0.8, 1.6)	185	0.92 (0.5, 1.7)

*Definitions of Abbreviations:* BD, bronchodilator; CI, confidence interval; cigs/day, cigarettes per day; FEV<sub>1</sub>/FVC, the ratio between the forced expiratory volume in one second and forced vital capacity.  

\* $p < 0.05$  \*\* $p < 0.01$  \*\*\* $p < 0.001$

$\Delta$  Criteria was fulfilled by 237 (3.9%) of offspring when seven-years-old, and 90 (9.3%) when 45 years old  
† Reference group are non-asthmatic individuals for whom neither parent smoked at least six days a week, at age seven  
‡ Multivariable model adjusted for sex, father's occupation, parental history of asthma/allergy, childhood asthma severity  
§ Multivariable model adjusted for sampling weights, sex, father's occupation, parental history of asthma/allergy, pre-BD FEV<sub>1</sub>/FVC at age 7 years (z-score < -1.64), SHS exposure in middle-age (<4 versus 4+ hours/day) and personal smoking (<1 versus  $\geq 1$  pack-year)

**TABLE 5: MULTIVARIABLE ASSOCIATIONS WITH CONTINUOUS FEV<sub>1</sub>/FVC LEVELS**

Parental smoking intensity when participants were aged 7	Ratio of FEV <sub>1</sub> /FVC			
	Childhood pre-BD airflow limitation (aged 7) ‡		Mid-life post-BD airflow obstruction (aged 45) §	
	N = 6,119	z-score (95%CI)	N = 972	z-score (95%CI)
<b>Maternal</b>				
Non-current smoker †	3,852	Ref	619	Ref
Light current (< 6 cigs/day)	355	-0.07 (-0.2 to +0.03)	64	-0.05 (-0.3 to +0.2)
Moderate current (6-20 cigs/day)	1,536	-0.07 (-0.1 to -0.01) *	226	+0.00 (-0.1 to +0.2)
Heavy current (> 20 cigs/day)	376	-0.18 (-0.3 to -0.1) ***	63	-0.33 (-0.6 to -0.1) *
<b>Paternal</b>				
Non-current smoker †	2,391	Ref	405	Ref
Light current (< 6 cigs/day)	225	+0.01 (-0.1 to +0.1)	43	+0.01 (-0.1 to +0.2)
Moderate current (6-20 cigs/day)	2,246	+0.02 (-0.03 to +0.1)	339	-0.02 (-0.2 to +0.1)
Heavy current (> 20 cigs/day)	1,257	+0.01 (-0.1 to +0.1)	185	-0.05 (-0.3 to +0.2)

*Definitions of Abbreviations:* BD, bronchodilator; CI, confidence interval; cigs/day, cigarettes per day; FEV<sub>1</sub>/FVC, the ratio between the forced expiratory volume in one second and forced vital capacity.  
 \*p<0.05 \*\*p<0.01 \*\*\*p<0.001  
 A z-score describes deviation from the mean predicted value, and has a mean of 0 and a standard deviation of 1 in the reference population  
 † Reference group are non-asthmatic individuals for whom neither parent smoked at least six days a week, at age seven  
 ‡ Multivariable model adjusted for sex, father's occupation, parental history of asthma/allergy, childhood asthma severity  
 § Multivariable model adjusted for sampling weights, sex, father's occupation, parental history of asthma/allergy, childhood asthma/wheezy breathing at age 7, pre-BD FEV<sub>1</sub>/FVC at age 7 years (z-score), SHS exposure in middle-age (up to 4 versus 4+ hours/day) and personal smoking (<1 versus ≥1 pack-year)

**TABLE 6: SHS EXPOSURE AND GAS TRANSFER FACTOR AT AGE 45, STRATIFIED BY SEX**

		T <sub>L</sub> CO levels at age 45 (z-scores [95%CI]), by sex and male-smoking †			
		Females (n = 442)	Males (n = 469)		p <sub>int</sub> §
			Non-smokers	Ever-smokers	
Maternal smoking, at 7					
	Not exposed	Ref	Ref	- 0.18 (-0.4 to +0.0) <sup>^</sup>	0.015 ‡
	Exposed	- 0.08 (-0.3 to +0.1)	+ 0.06 (-0.2 to +0.3)	- 0.49 (-0.7 to -0.3) <sup>***</sup>	
Paternal smoking, at 7 ††					
	Not exposed	Ref	Ref	- 0.25 (-0.5 to -0.0) *	0.489
	Exposed	- 0.15 (-0.1 to +0.4)	+ 0.00 (-0.2 to +0.2)	- 0.35 (-0.6 to -0.1) **	

*Definitions of Abbreviations:* int, interaction; SHS, second-hand smoke; T<sub>L</sub>CO, single breath transfer factor of the lung for carbon monoxide.  
<sup>^</sup>p=0.053 \*p<0.05 \*\*p<0.01 \*\*\*p<0.001  
 † T<sub>L</sub>co values were adjusted to a standard haemoglobin concentration and corrected for the presence of carboxyhaemoglobin  
 † Multivariable adjusted model includes sampling weights, fathers/current occupation, lifetime asthma pattern, parental history of asthma/allergy, all SHS exposures including the interaction term maternal\*active smoking  
 ‡ The effect of active smoking on T<sub>L</sub>CO levels between males with and without maternal smoke exposure.  
 § Stratification by sex was not significant p>0.200  
 †† Maternal\*active smoking interaction was taken into account

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