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Tobacco smoke exposure in early life and adolescence in relation to lung function

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Maternal smoking *in utero* and teenage smoking are associated with indices of airway obstruction at age 16 years http://ow.ly/NwF030jFS2W

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ABSTRACT Maternal smoking during pregnancy is associated with impaired lung function among young children, but less is known about long-term effects and the impact of adolescents' own smoking. We investigated the influence of maternal smoking during pregnancy, secondhand smoke exposure and adolescent smoking on lung function at age 16 years.

The BAMSE (Barn/Child, Allergy, Milieu, Stockholm, Epidemiology) birth cohort collected information on participants' tobacco smoke exposure through repeated questionnaires, and measured saliva cotinine concentrations at age 16 years. Participants performed spirometry and impulse oscillometry (IOS) at age 16 years (n=2295).

Exposure to maternal smoking during pregnancy was associated with reduced forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ratio of −1.1% (95% CI −2.0 to −0.2%). IOS demonstrated greater resistance at 5–20 Hz ($R_{5–20}$) in participants exposed to maternal smoking during pregnancy. Adolescents who smoked had reduced FEV_1/FVC ratios of −0.9% (95% CI −1.8 to −0.1%) and increased resistance of 6.5 $Pa{\cdot}L^{-1}{\cdot}s$ (95% CI 0.7 to 12.2 $Pa{\cdot}L^{-1}{\cdot}s$) in $R_{5–20}$. Comparable associations for FEV_1/FVC ratio were observed for cotinine concentrations, using $\geqslant$12 $ng{\cdot}mL^{-1}$ as a cut-off for adolescent smoking.

Maternal smoking during pregnancy was associated with lower FEV_1/FVC ratios and increased airway resistance. In addition, adolescent smoking appears to be associated with reduced FEV_1/FVC ratios and increased peripheral airway resistance.

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Introduction

Despite continued health campaigns, tobacco smoking remains a pervasive problem and the harmful effects of tobacco smoking and secondhand smoke (SHS) exposure on morbidity and mortality are well established [1, 2]. Although the prevalence of tobacco smoking among adolescents is declining in high-income countries, the use of some tobacco products such as e-cigarettes has increased and these are often used in conjunction with cigarette smoking [3]. Many smokers try their first cigarette in early adolescence and establish habits that can persist into adulthood [4]. Exposure to tobacco smoking during the perinatal period has been consistently associated with impaired pulmonary function in infants and children, but less is known about how pulmonary function is affected in adolescence [5, 6]. In general, lung growth and functional development continues until the mid-twenties [7], and failure to reach maximal lung growth can have lasting deleterious effects [6, 8]. Data on the independent effect of adolescent smoking on lung function accounting for maternal smoking during pregnancy are limited, especially utilising prospectively collected data from birth to adolescence [9, 10]. Furthermore, it remains unclear whether interactions between exposure during pregnancy and personal smoking in adolescence exist.

The majority of studies use indices from spirometry to assess lung function, which is a more aggregate measure of airway resistance and large airway function [11]. Another method, impulse oscillometry (IOS) is an effort-independent technique used to assess lung function and can distinguish between peripheral and central airway dysfunction [12]. While many studies have relied on self-reported smoking in adolescence, few studies on lung function have used an objective biomarker such as saliva cotinine to discriminate adolescent smokers from nonsmokers [13].

We aimed to assess the associations between exposure to maternal smoking during pregnancy, SHS exposure in childhood and adolescent smoking on lung function at age 16 years. Additionally, we used saliva cotinine concentrations to determine smoking status and assess the association with lung function at age 16 years.

Methods

The present study utilises data collected within the Swedish BAMSE (Barn/Child, Allergy, Milieu, Stockholm, Epidemiology) study [14]. Briefly, 4089 children born between 1994 and 1996 were recruited and followed from birth to age 16 years. At enrolment, when participants were a median age of 2 months, parents completed a questionnaire which queried information on environmental and lifestyle factors such as parental smoking. Subsequent questionnaires were completed by parents at ages 1, 2, 4, 8, 12 and 16 years, and included questions concerning smoking habits of parents. At ages 12 and 16 years, in addition to parental questionnaires, participants completed their own questionnaires. Follow-up response rates were 96%, 94%, 91%, 84%, 82% and 78%, respectively.

Following the completion of questionnaires at age 16 years, adolescents were invited to participate in clinical examinations including lung function testing.

Exposure to tobacco smoke was ascertained by repeated questionnaires throughout childhood and adolescence.

Maternal smoking during pregnancy was defined as the mother smoking ⩾1 cigarettes per day at any trimester of pregnancy and to assess dose-response effects we categorised the number of cigarettes smoked by the mother into three categories: 1) no cigarettes throughout pregnancy (reference category); 2) 1–9 cigarettes per day during any trimester; and 3) ⩾10 cigarettes per day during any trimester [15].

SHS exposure during infancy was defined as the mother and/or father smoking ⩾1 cigarettes per day at enrolment.

SHS exposure at age 16 years was defined as the mother and/or father smoking ⩾1 cigarettes per day at the 16-year follow-up.

Adolescent smoking was defined as any smoking at age 16 years. This variable was further categorised into 1) occasional smokers (smoking <1 cigarette per day); and 2) daily smokers (smoking ⩾1 cigarette per day). Nonsmoking participants made up the reference group. In order to interpret the data on cotinine in saliva (see later), we obtained information on the use of smokeless tobacco (oral moist snuff, snus), which is commonly used in Sweden, especially by males [16]. Smokeless tobacco use was defined as occasional or daily use.

Indices of pulmonary function were analysed by spirometry and by IOS using the Jaeger MasterScreen-IOS system (Carefusion Technologies, San Diego, CA, USA). For spirometry indices, highest values of forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) were used [17, 18]. The

FEV_1/FVC ratios were expressed as percentages. Standard deviation scores for FEV_1, FVC and FEV_1/FVC were computed taking age, sex, height and ethnicity into account [19].

Information on the IOS system has been given in detail elsewhere [12, 17, 20, 21] and is provided in the online supplementary material. The mean value of resistance at 5 Hz (R_5), resistance at 20 Hz (R_{20}), frequency dependence of resistance ($R_{5–20}$) and the square root of the area of reactance ($AX^{0.5}$) were used in the final analyses.

Fractional exhaled nitric oxide (F_{ENO}) is a simple noninvasive test which reflects eosinophilic airway inflammation [22]. We used an Eco Medic instrument system (Eco Medics, Duernten, Switzerland) and single-breath technique was used according to the American Thoracic Society and European Respiratory Society guidelines [23].

Cotinine is a quantitative biomarker of recent uptake of nicotine, which may result from active or passive smoking and the use of smokeless tobacco products [24, 25]. Saliva samples were collected when participants were aged 16 years. Evening samples were analysed using the Salimetrics cotinine kit (Salimetrics Europe, Newmarket, UK) with a detection limit of 0.8 ng·mL^{-1}. The distribution of saliva cotinine concentrations in nonsmokers was positively skewed; therefore the data were log-transformed, and we assigned a value of 0.4, half the detection limit, to undetectable concentrations [24]. A cut-off of ⩾12 ng·mL^{-1} was used to discriminate adolescent smokers from nonsmokers [26].

Statistical analyses

The association between tobacco smoke exposure and spirometry indices was analysed using linear regression on the mean, and IOS indices with quantile regression (regression on the median) because the distribution of IOS values was positively skewed. Final models included sex, age and height as confounders (see online supplementary material). We tested a mutually adjusted model including maternal smoking during pregnancy, SHS exposure during infancy, SHS exposure at 16 years and adolescent smoking at 16 years. In addition, stratification by sex and by any wheeze in the past 12 months was conducted. Potential effect modification by maternal smoking during pregnancy on adolescent smoking at 16 years with lung function at 16 years was tested using an interaction model.

The final study population comprised participants with a valid spirometry measure, information on smoking habits at age 16 years and covariates (n=2295). For analyses related to saliva cotinine concentrations, participants with a valid spirometry measure, a saliva cotinine concentration and covariates were included (n=1523).

Statistical analyses were performed using STATA (release 12; Stata Corp, College Station, TX, USA).

Results

The selected study population (n=2295) had lower proportions of maternal smoking during pregnancy (11.1% *versus* 15.2%), parental smoking during infancy (19.6% *versus* 22.8%), parental smoking at 16 years (12.4% *versus* 16.7%) and male sex (47.6% *versus* 54.2%), as well as a higher proportion of parental allergic disease (32.1% *versus* 26.6%) and nonmanual workers (85.9% *versus* 78.6%) compared to excluded participants (n=1794) (online supplementary table E1).

A total of 254 (11.1%) participants were exposed to maternal smoking during pregnancy, 447 (19.6%) exposed to SHS during infancy and 271 (12.4%) exposed to SHS at age 16 years, while 280 (12.2%) were adolescent smokers (table 1). There was an overlap between maternal smoking during pregnancy, SHS at age 16 years and adolescent smoking, and 19.9% of the adolescent smokers were exposed to maternal smoking in pregnancy compared to 9.5% of the nonsmokers ($p<0.001$) (online supplementary figure E1). Additionally, at age 16 years, 27.6% of adolescent smokers had a parent who was smoking, compared to 10.4% of nonsmoking adolescents ($p<0.001$). Among the adolescent smokers, 102 (4.4% of the population) smoked daily while 178 (7.8% of the population) smoked occasionally. The mean age for smoking onset (⩾1 cigarette per week) was 14.7 years (range 11–17 years). The prevalence of adolescent smoking was comparable among males and females (11.8% *versus* 12.6%), while use of smokeless tobacco was more common among males than among females (8.9% *versus* 0.4%). Nearly two-thirds of those who used smokeless tobacco were also adolescent smokers. Saliva cotinine levels were higher among males than females (geometric mean 0.21 ng·mL^{-1} *versus* 0.13 ng·mL^{-1}), partly explained by the higher smokeless tobacco use among males.

Exposure to maternal smoking during pregnancy was associated with reduced FEV_1/FVC ratios at age 16 years of −1.1% (95% CI −2.0 to −0.2%) (table 2). In dose-response analyses, a significant trend for increasing number of cigarettes was observed (p_{trend} <0.01), with reduced FEV_1/FVC ratio (−1.8%, 95% CI −3.0 to −0.7) in participants exposed to ⩾10 cigarettes per day during pregnancy.

TABLE 1 Anthropometric and lung function characteristics as well as tobacco exposure among children at age 16 years in the BAMSE (Barn/Child, Allergy, Milieu, Stockholm, Epidemiology) cohort

		Males		Females
Age years	1092	16.7±0.4	1203	16.7±0.4
Height m	1092	1.8±0.07	1203	1.7±0.06
FEV_1 mL	1052	4501.8±644.5	1175	3484.9±443.6
FEV_1 z-score	1051	−0.03±0.96	1175	−0.04±0.90
FVC mL	969	5382.7±778.6	1140	4037.6±526.0
FVC z-score	968	0.15±0.95	1140	0.15±0.88
FEV_1/FVC %	929	83.8±6.6	1112	86.5±6.1
FEV_1/FVC z-score	929	−0.30±0.98	1112	−0.36±0.95
Saliva cotinine level[#] ng·mL^{-1}	706	0.21±10.0	817	0.13±7.0
R_5–R_{20}[¶] Pa·L^{-1}·s	1051	15.0 (45.0)	1143	20.0 (55.0)
$AX^{0.5}$[¶] Pa·L^{-1}	1050	12.6 (5.0)	1143	16.4 (5.8)
F_{ENO}[¶] ppb	1081	16.0 (14.1)	1188	12.8 (10.4)
Maternal smoking during pregnancy[+]	1092	118[##] (10.8)	1202	136[##] (11.3)
SHS exposure during infancy[§]	1086	204[##] (18.8)	1194	243[##] (20.4)
SHS exposure at 16 years	1045	133[##] (12.7)	1137	138[##] (12.1)
Participant's smoking[f]	1092	129[##] (11.8)	1203	151[##] (12.6)
Participant's smokeless tobacco use[f]	1090	97[##] (8.9)	1199	5[##] (0.4)

Data are presented as n, mean±SD or n (%), unless otherwise stated. n=2295. FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; $R_{5–20}$: resistance at 5–20 Hz; $AX^{0.5}$: square root of the area of reactance; F_{ENO}: fractional exhaled nitric oxide; SHS: secondhand smoke. [#]: geometric mean; [¶]: median (interquartile range); [+]: ⩾1 cigarette per day during any trimester; [§]: mother or father smoking ⩾1 cigarette per day at enrolment (2 months); [f]: adolescent daily or occasional smoking or smokeless tobacco use; [##]: exposed subjects.

Exposure to maternal smoking during pregnancy or SHS during infancy was not significantly associated with lower values of FEV_1 or FVC at age 16 years. However, we observed small declines in FEV_1/FVC ratios in participants exposed to SHS during infancy (−0.6%, 95% CI −1.3 to 0.1%).

Compared to nonsmoking participants, adolescent smoking at age 16 years was associated with significantly lower FEV_1/FVC ratios of −0.9% (95% CI −1.8 to 0.1%). In analyses separated by smoking frequency, lower FEV_1/FVC ratios were found both among occasional (−1.1%, 95% CI −2.1 to −0.04%) and daily smokers (−0.7%, 95% CI −2.1 to 0.6%).

TABLE 2 Differences in lung function between exposed and unexposed participants to tobacco smoke and lung function at age 16 years

	Subjects n	FEV_1 mL Difference (95% CI)[#]	FVC mL Difference (95% CI)[#]	FEV_1/FVC % Difference (95% CI)[#]
Maternal smoking during pregnancy				
No	2040	Reference	Reference	Reference
Yes	254	−32.7 (−91.9 to −26.4)	16.1 (−54.0 to −86.2)	−1.1 (−2.0 to −0.2)
SHS exposure during infancy				
No	1833	Reference	Reference	Reference
Yes	447	−2.4 (−49.6 to −44.8)	20.2 (−35.0 to −75.4)	−0.6 (−1.3 to −0.1)
SHS exposure at 16 years				
No	1911	Reference	Reference	Reference
Yes	271	35.1 (−22.7 to −92.8)	65.0 (−3.9 to −133.9)	−0.7 (−1.5 to −0.2)
Participant's smoking				
Nonsmokers	2015	Reference	Reference	Reference
Adolescent smoking[¶]	280	−12.6 (−69.3 to −44.2)	16.6 (−50.1 to −83.3)	−0.9 (−1.8 to −0.1)
Occasional smokers	178	−34.4 (−103.6 to −34.8)	17.2 (−64.1 to −98.4)	−1.1 (−2.1 to −0.04)
Daily smokers	102	26.3 (−64.3 to 116.9)	15.6 (−91.2 to 122.3)	−0.7 (−2.1 to 0.6)

FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; SHS: secondhand smoke. [#]: calculated by linear regression on the mean adjusted for sex, age and height; [¶]: daily or occasional smoking.

In mutually adjusted models, which included maternal smoking during pregnancy, SHS exposure during infancy, SHS exposure at age 16 years and children's own smoking, FEV1/FVC ratios remained lower (although nonsignificantly so) in participants exposed to maternal smoking during pregnancy (−1.0%, 95% CI −2.1 to 0.02%) and among adolescent smokers at age 16 years (−0.8%, 95% CI −1.7 to 0.1%) (online supplementary table E2). There was no statistically significant interaction between maternal smoking during pregnancy and adolescent smoking for FEV1/FVC ratios (p=0.35). Nevertheless, participants who were exposed to both maternal smoking during pregnancy and adolescent smoking (n=58) had reduced FEV1/FVC ratios of −2.5% (95% CI −4.3 to −0.7%), and a tendency towards reduced FEV1/FVC ratios were observed for participants exposed to maternal smoking during pregnancy only and for adolescent smoking only, compared to nonexposed participants (online supplementary table E3).

We observed significant increases in airway resistance among participants exposed to maternal smoking during pregnancy (table 3). Compared to unexposed participants, those exposed to maternal smoking during pregnancy had significant increases in R_5 (13.1 $Pa{\cdot}L^{-1}{\cdot}s$, 95% CI 1.4 to 24.9 $Pa{\cdot}L^{-1}{\cdot}s$), $R_{5–20}$ (9.2 $Pa{\cdot}L^{-1}{\cdot}s$, 95% CI 2.8 to 15.6 $Pa{\cdot}L^{-1}{\cdot}s$) and $AX^{0.5}$ (0.7 $(Pa{\cdot}L^{-1}{\cdot}s)^{0.5}$, 95% CI 0.1 to 1.2 $(Pa{\cdot}L^{-1}{\cdot}s)^{0.5}$).

Among adolescent smokers we observed a significant increase in $R_{5–20}$ (6.5 $Pa{\cdot}L^{-1}{\cdot}s$, 95% CI 0.7 to 12.2 $Pa{\cdot}L^{-1}{\cdot}s$) at age 16 years, but not in R_5, R_{20} or $AX^{0.5}$ (table 3). In addition, adolescent smokers had significantly lower levels of F_{ENO} of −2.2 ppb (95% CI −3.4 to −0.9 ppb).

In general, participants exposed to any tobacco had higher geometric mean saliva cotinine concentrations compared to unexposed participants (figure 1). Excluding smokeless tobacco users and using $\geqslant$12 $ng{\cdot}mL^{-1}$ to discriminate adolescent smokers from nonsmokers, we correctly classified 97.6% of daily smokers (online supplementary table E4).

Online supplementary table E5 shows the results of using a cut-off of $\geqslant$12 $ng{\cdot}mL^{-1}$ to distinguish adolescent smokers from nonsmokers and the association with indices of lung function at age 16 years. Smokeless tobacco users were excluded in these analyses. Participants with a saliva cotinine concentration of $\geqslant$12 $ng{\cdot}mL^{-1}$ had reduced FEV1/FVC ratios of −1.5% (95% CI −2.5 to −0.4%) compared to children with <12 $ng{\cdot}mL^{-1}$ (online supplementary table E5).

In sensitivity analyses we tested if there was any interaction between any adolescent smoking and any wheeze at 16 years for FEV1/FVC ratios, but no significant interaction was observed (p=0.20), nor were apparent differences seen when stratified by wheeze (online supplementary table E6). However, we did find evidence of interaction between adolescent smoking and asthma at age 16 years for FEV1 and FEV1/FVC ratios (p=0.04 and p=0.05, respectively) and impaired lung function was observed among nonasthmatic smokers (online supplementary table E7). We observed no significant differences between males and females in stratified analyses (online supplementary table E8). Z-score analyses yielded analogous results to those seen in regular analyses (online supplementary table E9).

TABLE 3 Associations between tobacco smoke exposure and participant's lung function by impulse oscillometry and exhaled nitric oxide fraction (F_{ENO}) at age 16 years

	R_5 $Pa{\cdot}L^{-1}{\cdot}s$	R_{20} $Pa{\cdot}L^{-1}{\cdot}s$	$R_{5–20}$ $Pa{\cdot}L^{-1}{\cdot}s$	$AX^{0.5}$ $Pa{\cdot}L^{-1}$	F_{ENO} ppb
	Difference (95% CI)#	**Difference (95% CI)#**	**Difference (95% CI)#**	**Difference (95% CI)#**	**Difference (95% CI)#**
Maternal smoking during pregnancy					
No	Reference	Reference	Reference	Reference	Reference
Yes	13.1 (1.4 to 24.9)	4.5 (−5.3 to −14.2)	9.2 (2.8 to −15.6)	0.7 (0.1 to −1.2)	−0.8 (−2.2 to −0.6)
SHS exposure during infancy					
No	Reference	Reference	Reference	Reference	Reference
Yes	−3.4 (−12.8 to −6.1)	−2.1 (−9.9 to −5.7)	1.4 (−3.5 to −6.3)	0.2 (−0.3 to −0.6)	−0.3 (−1.4 to −0.7)
SHS exposure at 16 years					
No	Reference	Reference	Reference	Reference	Reference
Yes	−1.0 (−12.7 to −10.8)	−6.5 (−15.9 to −2.9)	4.5 (−1.5 to −10.5)	0.6 (0.1 to −1.2)	−0.8 (−2.0 to −0.5)
Participants smoking					
Nonsmokers	Reference	Reference	Reference	Reference	Reference
Adolescent smoking¶	−6.4 (−17.5 to −4.7)	−10.5 (−19.6 to −1.3)	6.5 (0.7 to −12.2)	0.3 (−0.3 to −0.8)	−2.2 (−3.4 to −0.9)

R_5: resistance at 5 Hz; R_{20}: resistance at 20 Hz; $R_{5–20}$: resistance at 5–20 Hz; $AX^{0.5}$: square root of the area of reactance; SHS: secondhand smoke. #: median difference in outcome compared to the reference group, calculated by linear regression on the median adjusted for sex, age and height; ¶: daily or occasional smoking.

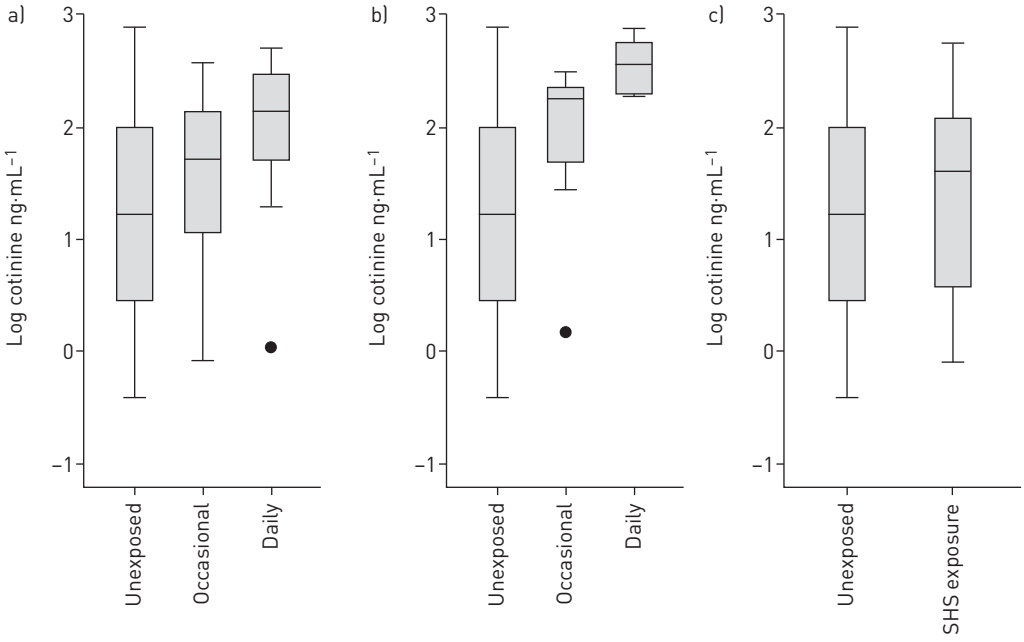

FIGURE 1 Distribution of saliva cotinine levels by a) adolescent smoking, b) smokeless tobacco use and c) secondhand smoke (SHS) exposure at age 16 years. Restricted to those children with detectable cotinine (n=179). Unexposed category are those participants who were unexposed to adolescent smoking, SHS exposure at 16 years and smokeless tobacco.

Discussion

In this prospective birth cohort, maternal smoking during pregnancy was associated with lower FEV1/FVC ratios in the offspring at age 16 years. In addition, our findings indicate that exposure to maternal smoking during pregnancy increases peripheral airway resistance shown by IOS indices. A tendency of an association between adolescent smoking at age 16 years was also associated with lower FEV1/FVC ratios and increased peripheral airway resistance, suggesting early signs of airflow obstruction. We observed no significant associations between SHS exposure during infancy or at age 16 years with lung function at age 16 years.

This is one of few prospective studies that assesses exposure to maternal smoking during pregnancy and concurrently accounts for exposure to adolescent smoking in relation to lung function in adolescents. Our finding for decreased FEV1/FVC ratios in children exposed to maternal smoking during pregnancy corroborates some prior studies [27–29], whereas other studies have found declines in FEV1 or FVC, which were not observed in the present study [30, 31]. Our results confirm and extend those from the Isle of Wight cohort, which also found reduced FEV1/FVC ratios among adolescents (mean age 18 years) exposed to maternal smoking during pregnancy [28]. However, this study did not assess the association between adolescent smoking and lung function. Additionally, in a cohort of 519 participants, Guerra *et al.* [9] observed an early accelerated decline in FEV1/FVC ratios in 26-year-olds, but only in subjects exposed to both adolescent smoking and maternal smoking during pregnancy.

To our knowledge this is the first study to show the association between maternal smoking during pregnancy and indices from IOS in adolescents. We observed significant increases in peripheral airway resistance in adolescents exposed to maternal smoking during pregnancy. This is supported by previous studies which found reduced forced expiratory flow at 25–75% of FVC, which is indicative of airflow in small airways [28, 31].

In addition, we observed lower FEV1/FVC ratios among adolescent smokers, which is consistent with some [4, 32], but not all [7, 9] previous studies on adolescents. Based on lung function from IOS measures we observed increased airway resistance at 5–20 Hz, which is suggestive of small airway impairment. It is challenging to separate the effects of maternal smoking during pregnancy from adolescent smoking; however, we observed nonsignificant declines in lung function following adjustment for maternal smoking during pregnancy, as well as a tendency towards reduced FEV1/FVC ratio in adolescent smokers without prior exposure to maternal smoking during pregnancy.

A unique and novel aspect of our study was the use of saliva cotinine concentrations in adolescents in relation to lung function. Implementing a $\geqslant$12 ng·mL^{-1} cut-off as a biomarker of adolescent smoking, we

confirmed our finding of reduced FEV_1/FVC ratios among smoking participants. We found that some individuals who reported not smoking were above the 12 $ng \cdot mL^{-1}$ cut-point. These individuals could have been highly exposed to SHS, or did not report accurately. Additionally, some participants' cotinine concentrations fell below the cut-point, but still indicated they were occasional smokers. This is probably because they smoked infrequently or do not inhale sufficiently to increase the cotinine concentration. Both sex and symptoms of wheeze have been suggested to influence the effect of tobacco smoke exposure on lung function, but we saw no evidence of this [4, 31, 33].

Few studies on tobacco smoke exposure and lung function have used both spirometry and IOS to assess lung function, and to our knowledge none have assessed saliva cotinine concentrations to discriminate smoking status in relation to lung function in adolescents. The high participation rate and long follow-up, which extended from birth to age 16 years, are additional strengths and essential in understanding influential periods of exposure and causal associations.

Our findings should be interpreted in the context of some limitations. The use of questionnaires to ascertain smoking habits from parents and participants has the potential for misreporting. The saliva cotinine concentrations suggested that there is likely some degree of underreporting of smoking among the participants. Nevertheless, we observed significantly lower FEV_1/FVC ratios in adolescent smokers, which could be an underestimation of the true effect. Although the sample size of the cohort included in the analysis is reasonably large, it is possible we were unable to detect significant associations in other indices of lung function due to statistical power, particularly in view of low prevalence rates of tobacco smoke exposure prenatally and during childhood.

Lung development begins during embryogenesis and alveolarisation continues into early adulthood. Tobacco smoke contains >4000 chemicals, many of which are detrimental to the respiratory system. Nicotine, which easily passes the placental barrier, is associated with impaired lung development [34, 35]. The precise mechanisms by which tobacco smoke impacts lung function and development remains unclear. Animal studies suggest that exposure to tobacco smoke during intrauterine life modifies the homeostatic epithelial–mesenchymal interaction in the developing alveolus, which results in the production of myofibroblasts in both the large and small airways, a hallmark of chronic lung disease [28]. Exposure to maternal smoking during pregnancy probably alters the structures and function of the lung during gestation, which in turn can permanently impact properties of the lung such as elastic recoil, smooth muscle and epithelial organisation [36]. We saw a tendency for increased FVC among participants exposed to maternal smoking during pregnancy as well as adolescent smoking, which has been suggested in other studies, and translates directly to a decline in FEV_1/FVC ratio [28, 29]. Exposure to maternal smoking during pregnancy can affect both airways and alveolar growth [37], but our results suggest the reduction is more pronounced in the airways, which is supported by increases in airway resistance.

Although participants exposed to maternal smoking during pregnancy more often smoked in adolescence, it is not clear if this is a causal association. Nicotine exposure during early brain development could influence nicotine addiction. Similarly, an indirect association is also plausible, since parental smoking after the child is born is more common in these families and could indirectly influence adolescent smoking behaviour [38]. Therefore, the consequences of maternal smoking during pregnancy are probably multifactorial.

Adolescents with pre-existing lung impairments may be particularly susceptible to the effects of smoking. Moreover, commencing smoking in adolescence is likely to negatively impact lung growth, and smoking among adults is causally associated with chronic obstructive pulmonary disease (COPD), lung cancer, pneumonia and chronic bronchitis [39]. In addition, the lungs of smokers show diffuse changes affecting the airway lining, epithelium and bronchiole structure [40].

Although a 1–2%-unit decline in FEV_1/FVC ratio may be small, impairments in lung function at an early age can limit the peak development in adulthood, and potentially set a course for COPD or other lung-related diseases. As such, our results add to the growing body of literature showing an influence of early life exposures on lung function development [10]. Since humans do not reach their maximal pulmonary function until their early twenties it remains necessary to further study the effects of tobacco smoking into adulthood [4].

In conclusion, we found that exposure to maternal smoking during pregnancy was associated with lower FEV_1/FVC ratios and increased airway resistance at age 16 years, indicating that perinatal tobacco smoke exposure has a persistent influence on lung function up to adolescence. In addition, our results suggest that adolescent smoking is associated with reduced FEV_1/FVC ratios and increased peripheral airway resistance, suggesting the development of airflow obstruction from only a short duration of smoking.

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Conflict of interest: None declared.

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