ORIGINAL ARTICLE

Combined effects of parental and active smoking on early lung function deficits: a prospective study from birth to age 26 years

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ABSTRACT

Background Cross-sectional reports have suggested that, among active smokers, previous exposure to parental smoking may increase susceptibility to development of chronic obstructive pulmonary disease. We assessed prospectively whether parental smoking enhances the effects of active smoking on early deficits of lung function in young adults.

Methods We used data from the prospective birth cohort, the Tucson Children's Respiratory Study. Maternal and paternal smoking was assessed via questionnaires completed by the parents at the time of the participant's birth. Active smoking by participants was assessed via personal questionnaires completed at ages 16 (YR16), 22 and 26 years. Four groups were generated based on the combination of parental and active smoking. Lung function parameters, including forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ratio, were assessed by spirometry before and after inhalation of 180 μg of albuterol at YR11, YR16, YR22 and YR26.

Results Complete data were available for 519 participants. Pre-bronchodilator FEV_1/FVC values did not differ at YR11, YR16 or YR22 by parental or active smoking. However, at YR26 participants with exposure to parental and active smoking had pre-bronchodilator FEV_1/FVC levels that were, on average, 2.8% (0.9% to 4.8%; p=0.003) lower than participants who were not exposed to parental or active smoking. In contrast, subjects who were only exposed to active smoking or only exposed to parental smoking did not differ from those who were not exposed to either. Between YR11 and YR26, participants with exposure to parental and active smoking had the steepest decline in sex, age and height adjusted residuals of FEV_1/FVC, FEV_1, forced expiratory flow between 25% and 75% of the FVC ($FEF_{25–75}$) and $FEF_{25–75}$/FVC (all p values between 0.03 and <0.001).

Conclusions Parental and active smoking act synergistically to affect early lung function deficits in young adulthood.

Key messages

What is the key question?
- Does exposure to parental smoking in childhood enhance the effects of active smoking on early deficits of lung function in young adult age?

What is the bottom line?
- We found that parental and active smoking act synergistically to affect early lung function deficits in young adulthood.

Why read on?
- These findings suggest that targeted smoking cessation efforts directed to young smokers who were exposed to parental smoking may be warranted and could result in reductions in the incidence of chronic obstructive pulmonary disease.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a leading cause of death in high-income countries, accounting for a significant proportion of total mortality,[1] and its public health burden is rapidly expanding worldwide.[2] The main preventable factor associated with COPD is tobacco smoking.[3] Although the rate of lung function decline in COPD is highly variable once the disease has occurred,[4] longitudinal studies have shown that the accelerated decline in lung function that is related to development of COPD may start shortly after the onset of smoking and that smokers who show early lung function declines are at the highest risk for early, severe disease.[5]

The factors that determine this early, accelerated lung function decline in susceptible smokers are not understood. It has been hypothesised that among the determinants of susceptibility to COPD are exposures and events occurring in utero and during the first years of life.[6 7] Burrows and coworkers showed that smokers with a history of recurrent respiratory illnesses during childhood were at increased risk for the development of COPD in adult life.[3] More recently, two retrospective studies suggested that parental smoking may synergise with personal smoking to increase the risk of COPD. Upton and coworkers[8] studied the middle-aged offspring of couples who were originally assessed almost 30 years earlier when they were aged 45–64, at which time information on the parents' smoking was obtained by questionnaire. No information on smoking during pregnancy was gathered. Maternal and paternal smoking were associated with significantly lower levels of the forced

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expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ratio among smokers but not among non-smokers. However, offspring lung function was assessed only once at age 45 years in this study, and therefore it was not possible to determine when parental smoking may first impact lung function. Foreman and coworkers[9] found that maternal smoking, assessed retrospectively through offspring questionnaires, was reported by 70% of patients with early onset COPD compared with only 44% of older patients with COPD ($p<0.001$), although statistical significance was lost after adjusting for confounders.

The goal of this study was to assess prospectively whether parental smoking enhances the effects of active smoking in determining very early deficits in lung function in young adults.

METHODS

Study population

The Tucson Children's Respiratory Study (CRS) is a prospective birth cohort study that enrolled 1246 healthy, unselected newborns between 1980 and 1984.[10] Shortly after the child's birth, parents completed a questionnaire describing their ethnicity, history of physician-diagnosed asthma, years of education and current smoking habits (including number of cigarettes smoked per day). They subsequently completed up to six follow-up questionnaires on their child's health taken approximately every 2 years until the child was 13 years old. Starting with the survey at age 16 (YR16), participants also completed follow-up questionnaires themselves, which included specific questions on their health and active smoking habits.

Early wheezing phenotypes were identified based on the combination of wheezing lower respiratory illness in the first 3 years of life and active wheezing at age 6 years, as previously described.[11] Physician-confirmed asthma and current wheeze in the previous year were assessed from questionnaires at each follow-up survey and active asthma was defined as physician-confirmed asthma plus at least one asthma attack in the previous year.

Skin prick tests and spirometric lung function tests (before and after the administration of 180 µg of albuterol via an aerochamber holding device) were performed at YR11, YR16, YR22 and YR26, as described previously[12] and in the online supplement. Spirometry parameters included FEV_1, FVC, and forced expiratory flow between 25% and 75% of the FVC ($FEF_{25–75}$). Ratios between FEV_1 and FVC and between $FEF_{25–75}$ and FVC were computed. Because the FEV_1/FVC ratio is the most widely used indicator of airflow limitation and smoking-related obstructive lung diseases,[13] this parameter was predefined as the primary outcome of our study.

Informed consent was obtained from the parents for their children, or from the enrolees themselves if appropriate, at each survey and the Institutional Review Board of the University of Arizona approved the study.

Smoking variables

We defined maternal, paternal and parental (ie, either parent) smoking based on the report of current smoking at the enrolment questionnaire (ie, at the time of participant's birth), which has provided the strongest signal of association with subsequent children's respiratory health[14] and immune responses[15] in previous studies on this cohort. In our study population, only 62 subjects had parents who did not smoke at the child's birth but smoked sometime by YR11 and only two subjects had parents who smoked when the participant was born but did not smoke between birth and YR11. Thus, our study was not powered to distinguish prenatal from postnatal effects of exposure to parental smoking, and we elected to use parental smoking at the child's birth in all analyses. Cumulative pack-years smoked by the parents between the child's birth and YR11 were computed based on questionnaire information as previously described,[15] and used in statistical models for sensitivity analyses.

Active smoking by the participant was defined as a positive report of current smoking by the enrolee at YR16, YR22 or YR26. Pack-years at YR26 were computed based on questionnaire information on usual number of cigarettes smoked per day and age at starting/quitting smoking.

Four combination groups were generated based on parental and active participant smoking as illustrated in online supplementary figure E1 (No parental smoking/No active smoking; No parental smoking/Yes active smoking; Yes parental smoking/No active smoking; and Yes parental smoking/Yes active smoking) and used as the main exposure variable in analyses. Similar combination groups with active smoking were generated for maternal and paternal smoking separately and used in secondary analyses.

Statistical analyses

Categorical variables were compared across groups with χ^2 analysis and continuous variables with analysis of variance (ANOVA) or non-parametric tests as appropriate.

To standardise the results of lung function tests within and between surveys, residuals were computed for all spirometry parameters by regressing at each survey raw values against sex, age and height at the time of testing. These residuals were then compared across parental smoking, active smoking and combination groups with ANOVA. To evaluate linear trends over time, available residuals for each spirometric parameter obtained at YR11, YR16, YR22 and YR26 for each individual participant were regressed against age at the time of each of these surveys and the corresponding β coefficients (ie, slopes) saved. Only subjects who had at least two lung function measurements (ie, 94% of the study population) were included. Participants' coefficients were then compared across parental smoking, active smoking and combination groups with non-parametric tests (Kruskal–Wallis).

To compare FEV_1/FVC levels and trends over time across smoking groups while adjusting for the intra-subject serial correlation of repeated observations and reducing the impact of missing observations, random coefficients models[16 17] were used. In these models, absolute values of FEV_1/FVC ratios (in percentage) from YR11, YR16, YR22 and YR26 were included as the dependent variable. In addition to other covariates, the independent variables included an indicator variable for survey, an indicator variable for the combination smoking groups, and interaction terms between survey and the combination groups to test for the effects of smoking varying at different surveys. Linear contrasts were then used to compare FEV_1/FVC values across parental and active smoking combinations at different surveys and to formally test the significance of interactions between parental and active smoking in affecting FEV_1/FVC values at different surveys.

Two-sided p values of less than 0.05 were regarded as significant. Statistical analyses were done with SPSS for Windows (V.18.0) and STATA (V.10.0).

RESULTS

Data from at least one lung function test in adult age (YR22 or YR26) and complete information on maternal, paternal and active smoking were available from 519 participants. They differed from other CRS participants based on parental factors that

are related to the likelihood of continuing to participate in the study, including education, ethnicity, smoking and age (table 1). Participants included in this study did not differ from other participants with regard to sex, wheezing status, asthma or skin prick test results.

Overall, 32% of participants (168/519) had at least one parent who smoked at the child's birth. As shown in table 2, participants whose parents smoked were more likely to smoke themselves than were participants with parents who did not smoke. However, among participants who smoked no significant differences were found in usual number of cigarettes smoked or in cumulative pack-years smoked by YR26 between participants with parents who smoked and those whose parents did not smoke.

Lung function data were available from 426 participants at YR11, 382 at YR16, 453 at YR22 and 350 at YR26 for a total of 1611 observations. Maternal and paternal smoking separately tended to be associated with linear trends of FEV_1/FVC residuals between YR11 and YR26 (see online supplementary table E1). However, when combinations between parental and active smoking were studied rates of decline in FEV_1/FVC were significantly different across groups, with subjects exposed to both parental and active smoking being consistently found to be the group with the steepest decline ($p=0.002$ and $p=0.007$ for combination variables of active with maternal and paternal smoking, respectively). In view of these results, we elected to use combination groups generated using any parental smoking (ie, smoking by either parent) in all subsequent analyses.

Neither parental smoking nor active smoking alone was associated with baseline FEV_1/FVC residuals at YR11, YR16 or YR22 (table 3). However, they were associated with significantly greater decline of FEV_1/FVC residuals between YR11 and YR26. When exposures were combined, participants who were exposed to parental and active smoking had the lowest FEV_1/FVC residuals at YR26 (ANOVA $p=0.047$) and the most negative temporal trend in FEV_1/FVC residuals among the four groups ($p=0.002$). Post-bronchodilator FEV_1/FVC residuals showed similar associations to those observed for baseline FEV_1/FVC ratios but effects were weaker and did not reach statistical significance (table 4).

Similarly, when linear trends of residuals for other lung function parameters were tested across the four combination groups, participants with exposure to parental and active smoking had significantly steeper declines for pre-bronchodilator, but not post-bronchodilator, FEV_1, $FEF_{25–75}$ and $FEF_{25–75}$/FVC (see online supplementary tables E2 and E3).

Consistent with the cross-sectional analyses, in longitudinal random coefficient models that included pre-bronchodilator FEV_1/FVC values at YR11, YR16, YR22 and YR26 as the dependent variable and were adjusted for sex, ethnicity, height, weight and survey, no significant differences in FEV_1/FVC values were found across the combination groups until participants reached age 26 (figure 1A). In these models, the group positive for parental and active smoking had significantly lower pre-bronchodilator FEV_1/FVC levels by age 26 compared with each of the other three combination groups (all p values between 0.003 and 0.007, figure 1A). A significant interaction between parental and active smoking was found at YR26 ($p=0.02$), indicating that active smoking interacts with parental smoking in affecting early FEV_1/FVC deficits in adult life. Results were similar but effects were weaker for post-bronchodilator FEV_1/FVC ratio (figure 1B), and the interaction between parental and active smoking at YR26 did not reach statistical significance ($p=0.11$).

Results on pre-bronchodilator FEV_1/FVC were confirmed after further adjustment for maternal age and education, paternal age and education, and participants' physician confirmed childhood asthma at age 22/26. In addition, in models restricted to subjects who smoked, parental smoking was associated with a 2.9% (0.6–5.3%; $p=0.01$) deficit in FEV_1/FVC ratio after further adjustment for personal pack-years smoked by age 26. Similarly, among subjects who were exposed to parental

Table 1 Comparison between participants in this study and all others enrolled in the Children's Respiratory Study (CRS)

		CRS participants included in this study (N=519)	All other CRS participants (N=727)	p Value
Sex	% Female	51.3	50.5	0.79
Ethnicity	% Non-Hispanic White	63.6	55.6	0.005
Wheezing phenotypes by age 6 years	% Never	49.4	53.8	
	% Early transient	22.9	16.4	
	% Late	15.2	14.8	
	% Persistent	12.5	15.1	0.10
Skin prick tests YR11	% Positive	55.2	54.7	0.90
Skin prick tests YR16	% Positive	70.5	74.0	0.45
Active MD asthma YR11	% Positive	12.9	13.2	0.90
Active MD asthma YR16	% Positive	13.9	13.7	0.96
Maternal				
Ever MD asthma	% Positive	10.0	11.8	0.33
Smoking	% Positive	14.6	19.9	0.02
Education	≤12 years	24.7	36.8	<0.001
Age at child's birth	Mean±SD	27.7±4.6	26.9±4.8	0.001
Paternal				
Ever physician-confirmed asthma	% Positive	11.8	12.3	0.78
Smoking	% Positive	26.8	34.8	0.003
Education	≤12 years	24.9	33.1	0.002
Age at child's birth	mean±SD	30.1±6.0	29.3±5.5	0.02

YR11, age 11 years; YR16, age 16 years.

Table 2 Relation of maternal, paternal and parental smoking with active smoking for the 519 participants in this study

	Mother smoked at child's birth			Father smoked at child's birth			Any parent smoked at child's birth		
	No	Yes	p Value	No	Yes	p Value	No	Yes	p Value
N	443	76		380	139		351	168	
YR16 (N=387)									
% Participants smoked at age 16	9.6	21.8	0.008	9.1	17.6	0.02	9.2	16.0	0.05
Usual N cigarettes smoked at age 16* median (IQR)	3 (0.4–8)	7 (4.5–10)	0.04	3 (1–6.5)	6 (1–10)	0.22	3 (1–8)	6 (1–10)	0.35
YR22 (N=499)									
% Participants smoked at age 22	25.5	45.1	0.001	24.1	39.6	0.001	22.3	40.7	<0.001
Usual N cigarettes smoked at age 22* median (IQR)	7 (2–12)	10 (5–12)	0.11	7 (2–13.5)	10 (4–11)	0.39	7 (1.5–13.5)	10 (3–12)	0.26
YR26 (N=464)									
% Participants smoked at age 26	21.7	41.2	0.001	21.2	33.3	0.007	20.2	33.6	0.002
Usual N cigarettes smoked at age 26* median (IQR)	5 (2–15)	8.5 (5–11)	0.35	5 (2–15)	9 (4–13)	0.20	5 (2–15)	8.5 (4–13)	0.28
YR16 to YR26 (N=519)									
% Participants ever smoked between age 16 and 26	31.6	52.6	<0.001	30.8	45.3	0.002	29.1	46.4	<0.001
N pack-years smoked by age 26 years* median (IQR)	2.9 (0.8–7.0)	3.7 (1.7–6.6)	0.25	2.7 (0.8–6.9)	3.8 (1.4–7.0)	0.22	2.7 (0.8–7.0)	3.7 (1.2–6.7)	0.25

*Computed only among active smokers.
YR16, age 16 years; YR22 age 22 years; YR26, age 26 years.

smoking, active smoking was associated with a 3.0% (0.7–5.3%; p=0.01) FEV_1/FVC deficit after further adjustment for usual number of cigarettes smoked by mother and father at child's birth and for number of pack-years that parents smoked between child's birth and YR11. These results indicate that the combined effects of parental and active smoking on FEV_1/FVC in early adult life cannot be simply ascribed to residual confounding by level of exposure to parental or active smoking.

DISCUSSION

The main finding of this study is that early accelerated decline in pre-bronchodilator lung function among young smoking adults is only observed among those whose parents smoked: by the age of 26 years, the FEV_1/FVC ratio in these subjects was approximately 3% lower than the ratio of active smokers not exposed to parental smoking, the ratio of non-smokers whose parents smoked, and the ratio of non-smoking participants whose parents did not smoke. Similar but weaker effects were observed for post-bronchodilator FEV_1/FVC ratio.

There are several points of our study that are worth noting. This is the first study in which parental and offspring smoking was assessed longitudinally from birth up to the offspring's early adult years. We previously reported[18] that, to assess the validity of parental questionnaire data at the child's birth, cotinine levels were measured in cord serum of a representative sample of 175 newborns. We concluded that our population misclassification of smoking mothers as non-smokers was approximately 1.5%.[18] For assessment of participants' smoking, in this study we used data obtained longitudinally through questionnaires completed at YR16, YR22 and YR26. Because not all subjects responded to all three questionnaires, we considered any participant's acknowledgment of being an active smoker in any of these questionnaires as sufficient evidence to include the subject in the current smoking category. While this could introduce some misclassification into the analysis, most likely it would bias our results towards the null. Thus, it is unlikely that our results could be attributable to recall bias, report bias or smoking deception.

A weakness of our study is that, due to the high mobility of the US population, many active participants in our study have left the state of Arizona and, therefore, their lung function could not be tested unless they voluntarily travelled back to Tucson. The remaining 519 subjects were from families of higher socioeconomic status, more likely to be non-Hispanic white and with parents who were less likely to smoke. However, there were no differences in the incidence of lower respiratory illnesses in early life or in the prevalence of asthma or allergies during childhood between participants included in this study and those who were not included. Our study was not powered to dissect the individual contributions of maternal versus paternal smoking in modifying the effects of active smoking on lung function (eg, only 15 active smokers had the mother who smoked and the father who did not). We were also unable to distinguish the potential effects of smoking during pregnancy from those of postnatal environmental tobacco smoke due to the paucity of parents who changed smoking behaviour. However, the fact that paternal smoking showed measurable effects on lung function decline in this and other studies[8 9] suggests that the effects observed may be due to active and passive maternal smoking during pregnancy, possibly in combination with postnatal exposure.

Our data suggest that the combined effects of parental smoking and active smoking on the development of airflow limitation and accelerated lung function decline may start very early in adult life. We found no significant difference in any lung function parameter at YR11 or YR16 between children whose parents smoked and those whose parents did not (tables 3 and 4). Meta-analyses[19] have shown a small effect of maternal smoking during pregnancy on schoolchildren's lung function, but our study was not powered to detect such an effect. In our analysis, the association between parental smoking and lung function first became noticeable (albeit non-significantly) at YR22 and became significant at YR26, but only among active smokers. These results thus suggest that the synergistic effects are not mainly the result of consecutive, additive lesions, with the one from parental smoking occurring first followed by the

Table 3 Mean and 95% CIs of baseline (before bronchodilator) forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) residuals at age 11, 16, 22 and 26 years and of their linear trends between age 11 and 26 years across parental and active smoking groups

		FEV_1/FVC residuals YR11		FEV_1/FVC residuals YR16		FEV_1/FVC residuals YR22		FEV_1/FVC residuals YR26		Linear trends of FEV_1/FVC residuals per year from YR11 to YR26	
		N	Mean (95% CI)	N	Mean (95% CI)	N	Mean (95% CI)	N	Mean (95% CI)	N	Mean (95% CI)
Parental smoking											
No		289	0.18 (−0.55 to 0.91)	258	0.21 (−0.62 to 1.05)	304	0.28 (−0.47 to 1.02)	235	0.47 (−0.34 to 1.28)	328	−0.01 (−0.07 to 0.06)
Yes		137	−0.38 (−1.33 to 0.56)	124	−0.44 (−1.55 to 0.67)	149	−0.57 (−1.65 to 0.51)	115	−0.97 (−2.12 to 0.18)	160	−0.08 (−0.15 to −0.01)
p Value			0.37		0.37		0.20		0.04		0.02
Active smoking, 16–26 years											
No		279	−0.04 (−0.74 to 0.67)	255	−0.15 (−0.97 to 0.67)	300	0.16 (−0.58 to 0.90)	230	0.39 (−0.44 to 1.22)	321	0.02 (−0.04 to 0.08)
Yes		147	0.07 (−0.94 to 1.08)	127	0.30 (−0.86,1.46)	153	−0.31 (−1.41 to 0.78)	120	−0.74 (−1.84 to 0.35)	167	−0.13 (−0.23 to −0.04)
p Value			0.86		0.54		0.47		0.11		0.001
Combined smoking groups											
Parental	Active, 16–26 years										
No	No	203	0.15 (−0.70 to 1.00)	188	−0.07 (−1.06 to 0.92)	220	0.28 (−0.58 to 1.14)	169	0.49 (−0.51 to 1.48)	233	0.03 (−0.04 to 0.10)
No	Yes	86	0.26 (−1.18 to 1.69)	70	0.97 (−0.62 to 2.57)	84	0.29 (−1.24 to 1.81)	66	0.45 (−0.97 to 1.86)	95	−0.10 (−0.25 to 0.04)
Yes	No	76	−0.54 (−1.84 to 0.76)	67	−0.36 (−1.86 to 1.13)	80	−0.16 (−1.66 to 1.34)	61	0.12 (−1.44 to 1.68)	88	−0.01 (−0.10 to 0.08)
Yes	Yes	61	−0.19 (−1.60 to 1.22)	57	−0.53 (−2.25 to 1.19)	69	−1.04 (−2.64 to 0.55)	54	−2.20 (−3.89 to −0.51)	72	−0.18 (−0.29 to −0.06)
p Value			0.82		0.56		0.52		0.047		0.002

YR11, age 11 years; YR16, age 16 years; YR22 age 22 years; YR26, age 26 years.

Table 4 Mean and 95% CIs of post-bronchodilator forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) residuals at age 11, 16, 22 and 26 years and of their linear trends between age 11 and 26 years across parental and active smoking groups

		FEV_1/FVC residuals YR11		FEV_1/FVC residuals YR16		FEV_1/FVC residuals YR22		FEV_1/FVC residuals YR26		Linear trends of FEV_1/FVC residuals per year from YR11 to YR26	
		N	Mean (95% CI)	N	Mean (95% CI)	N	Mean (95% CI)	N	Mean (95% CI)	N	Mean (95% CI)
Parental smoking											
No		278	0.37 (−0.25 to 1.00)	255	0.06 (−0.64 to 0.76)	302	0.36 (−0.26 to 0.98)	225	0.36 (−0.36 to 1.09)	321	−0.01 (−0.08 to 0.06)
Yes		133	−0.77 (−1.65 to 0.11)	121	−0.13 (1.08 to 0.82)	147	−0.73 (−1.61 to 0.15)	115	−0.71 (−1.66 to 0.24)	156	−0.08 (−0.14 to −0.01)
p Value			0.04		0.75		0.049		0.08		0.18
Active smoking, 16–26 years											
No		267	−0.07 (−0.69 to 0.56)	250	−0.13 (−0.82 to 0.56)	298	0.12 (−0.49 to 0.74)	224	0.31 (−0.41 to 1.04)	314	−0.01 (−0.07 to 0.06)
Yes		144	0.12 (−0.75 to 0.99)	126	0.26 (−0.71 to 1.23)	151	−0.24 (−1.15 to 0.66)	116	−0.61 (−1.56 to 0.35)	163	−0.07 (−0.16 to 0.02)
p Value			0.72		0.52		0.50		0.14		0.054
Combined smoking groups											
Parental	Active, 16–26 years										
No	No	195	0.31 (−0.42 to 1.03)	185	−0.12 (−0.95 to 0.71)	219	0.41 (−0.31,1.13)	163	0.41 (−0.47 to 1.29)	229	−0.00 (−0.09 to 0.08)
No	Yes	83	0.50 (−0.67 to 1.67)	70	0.54 (−0.78 to 1.86)	83	0.22 (−1.02 to 1.46)	62	0.24 (−1.03 to 1.51)	92	−0.02 (−0.14 to 0.11)
Yes	No	72	−1.08 (−2.29 to 0.12)	65	−0.17 (−1.44 to 1.11)	79	−0.66 (−1.84 to 0.52)	61	0.06 (−1.20 to 1.31)	85	−0.02 (−0.11 to 0.06)
Yes	Yes	61	−0.39 (−1.72 to 0.94)	56	−0.10 (−1.56 to 1.37)	68	−0.81 (−2.17 to 0.55)	54	−1.58(−3.02 to −0.13)	71	−0.14 (−0.25 to −0.03)
p Value			0.18		0.84		0.26		0.13		0.16

YR11, age 11 years; YR16, age 16 years; YR22 age 22 years; YR26, age 26 years.

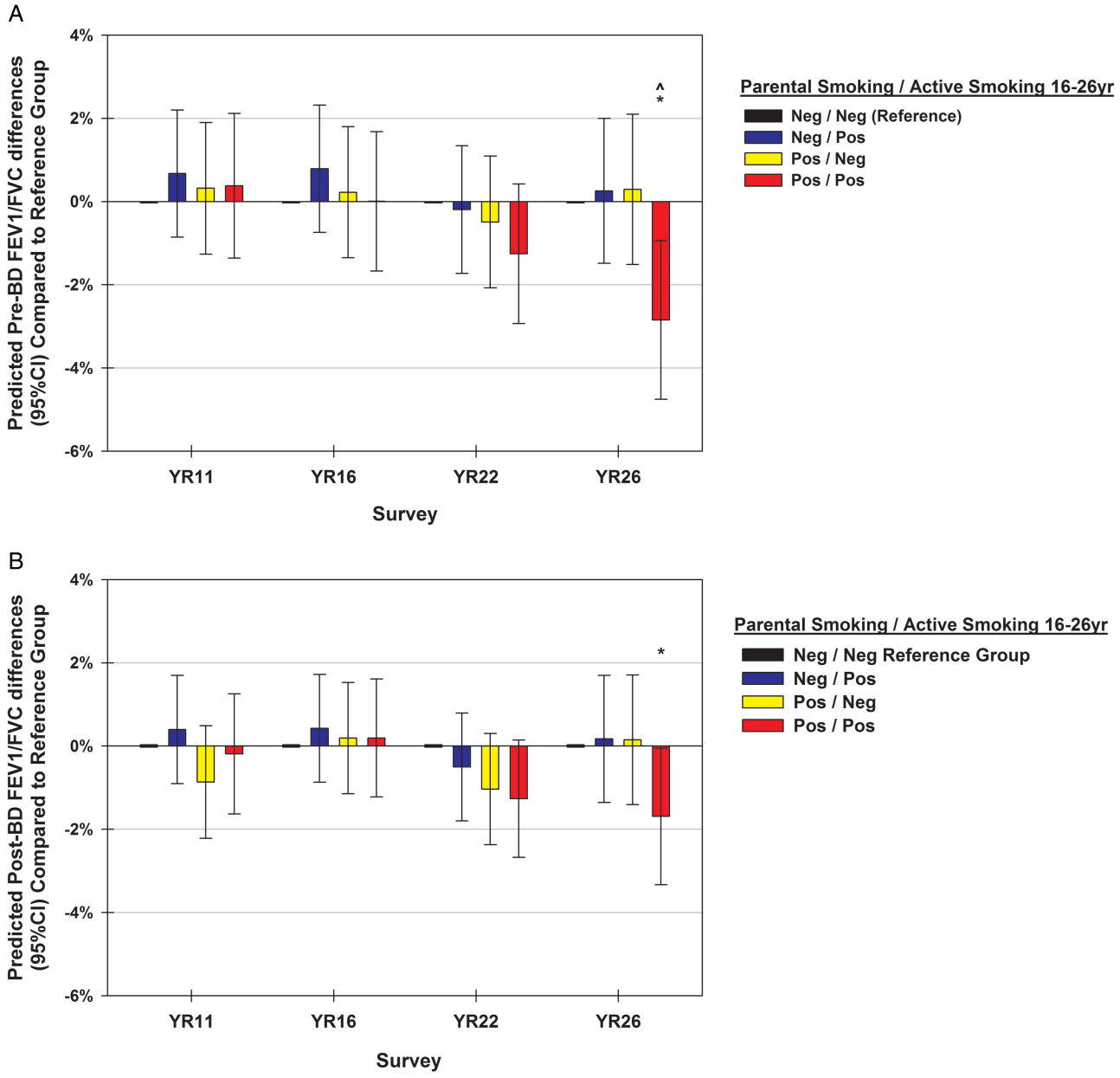

Figure 1 (A) Mean predicted differences in pre-bronchodilator forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) values (and their 95% CIs) between age 11 years (YR11) and YR26 across the different combination groups compared with the reference group of no parental smoking/no active smoking. Results shown are from random coefficients models including 519 subjects and 1611 PFT observations.* FEV_1/FVC values at YR26 for the Yes parental smoking/Yes active smoking group significantly lower than those of the following: No parental smoking/No active smoking group (mean difference 2.8%, 95% CI 0.9% to 4.8%; p=0.003); No parental smoking/Yes active smoking group (3.1%, 0.9% to 5.3%; p=0.006); Yes parental smoking/No active smoking group (3.1%, 0.9% to 5.4%; p=0.007).^ Significant interaction between parental and active smoking in affecting FEV_1/FVC values at YR26 (p=0.02). (B) Mean predicted differences in post-bronchodilator FEV_1/FVC values (and their 95% CIs) between YR11 and YR26 across the different combination groups compared with the reference group of No parental smoking/No active smoking. Results shown are from random coefficients models including 515 subjects and 1576 PFT observations.* FEV_1/FVC values at YR26 for the Yes parental smoking/Yes active smoking group lower than those of the following: No parental smoking/No active smoking group (1.7%, 0.1% to 3.3%; p=0.04); No parental smoking/Yes active smoking group (1.9%, −0.1% to 3.8%; p=0.06); Yes parental smoking/No active smoking group (1.8%, −0.1% to 3.8%; p=0.06). PFT, pulmonary function tests.

injury caused by active smoking on the airways. More likely, parental smoking causes small, direct effects in the lung or alterations in the airway response system, either of which may increase susceptibility to the deleterious effects of active smoking. Elliot *et al*[20] reported that inner airway wall thickness was greater in the larger airways of those infants who died of sudden infant death and whose mothers had smoked >20 cigarettes/day prenatally and postnatally than in those whose mothers had not. Compared with those without any exposure to cigarette smoke, the distance between alveolar attachments on airways was greater (p<0.001) in infants exposed to cigarette smoke in utero but not in those with only postnatal exposure.[21] Nicotine administered to rhesus monkeys during pregnancy[22] interacted directly with nicotinic receptors on non-neuronal cells in the developing lung, and resulted in increased collagen expression surrounding large airways and vessels.

Persistence of these and other lung alterations due to early exposure to parental smoking into adult life could increase susceptibility to airflow limitation in adult smokers.[23]

Interestingly, we also report that the earliest detectable effects of smoking on lung function appear to be, to a significant extent, reversible, because effects of combined parental and active smoking were weaker for post-bronchodilator than for baseline lung function. These effects were independent of a diagnosis of asthma, and may explain why in longitudinal studies smokers who are able to quit during follow-up at a young age show considerable improvement in FEV_1 compared with non-smokers.[24] The mechanisms that determine the progression from reversible to non-reversible airway obstruction in COPD require further elucidation but may implicate inflammatory and non-inflammatory pathways.[25]

In summary, our results suggest that exposure to tobacco products during lung development has long-term effects on the susceptibility of adult subjects to the noxious effects of active smoking, and that these effects may not be limited to those directly attributable to maternal smoking during pregnancy but could also be caused by passive cigarette smoking prenatally and postnatally. We conclude that, from a clinical perspective, targeted smoking cessation efforts directed at young smokers who were exposed to parental smoking may be warranted, and could result in reductions in the incidence of COPD.

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