Lifetime Risk Factors for Pre- and Post-Bronchodilator Lung Function Decline

A Population-based Study

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Abstract

Rationale: Interactions between early life and adult insults on lung function decline are not well understood, with most studies investigating prebronchodilator (pre-BD) FEV_1 decline.

Objectives: To investigate relationships between adult risk factors and pre- and post-BD lung function decline and their potential effect modification by early life and genetic factors.

Methods: Multiple regression was used to examine associations between adult exposures (asthma, smoking, occupational exposures, traffic pollution, and obesity) and decline in both pre- and post-BD spirometry (forced expiratory volume in 1 s [FEV_1], forced vital capacity [FVC], and FEV_1/FVC) between ages 45 and 53 years in the Tasmanian Longitudinal Health Study ($n = 857$). Effect modification of these relationships by childhood respiratory risk factors, including low childhood lung function and GST (glutathione S-transferase) gene polymorphisms, was investigated.

Results: Baseline asthma, smoking, occupational exposure to vapors/gases/dusts/fumes, and living close to traffic were associated with accelerated decline in both pre- and post-BD FEV_1. These factors were also associated with FEV_1/FVC decline. Occupational exposure to aromatic solvents was associated with pre-BD but not post-BD FEV_1 decline. Maternal smoking accentuated the effect of personal smoking on pre- and post-BD FEV_1 decline. Lower childhood lung function and having the GSTM1 null allele accentuated the effect of occupational exposure to vapors/gases/dusts/fumes and personal smoking on post-BD FEV_1 decline. Incident obesity was associated with accelerated decline in FEV_1 and more pronounced in FVC.

Conclusions: This study provides new evidence for accentuation of individual susceptibility to adult risk factors by low childhood lung function, GSTM1 genotype, and maternal smoking.

Keywords: lung function; decline; interaction; bronchodilator; susceptibility

(Received in original form April 23, 2019; accepted in final form December 3, 2019)

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This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org.

Ann Am Thorac Soc Vol ■■, No ■■, pp 1–11, ■■ 2020

DOI: 10.1513/AnnalsATS.201904-329OC
Internet address: www.atsjournals.org

Adult lung function declines gradually with age, but adverse adult exposures can accelerate the rate of decline (1). Accelerated lung function decline is increasingly recognized as a clinically important phenotype, as it worsens fixed airflow obstruction and is a major risk factor for chronic obstructive pulmonary disease (COPD) (1, 2), cardiovascular diseases (3), and all-cause mortality (4, 5).

Understanding the lifetime factors that contribute to accelerated lung function decline is critical to reduce these adverse outcomes. Although smoking is a well-known adult risk factor for accelerated lung function decline (1), there is some evidence that other adult factors, such as asthma, occupational exposures, and traffic pollution, may also be associated with increased risk (6–8). However, there is substantial individual variation in the rate of decline in those exposed to these factors, even among smokers, which suggests varying susceptibility between individuals. One potential reason for this variation is modification of the effect of adult exposures by genetic susceptibility and childhood risk factors (2). However, investigations of such interactions are limited (9).

Childhood factors may compound the effect of adult risk factors on adult lung function decline through early life programming and reduced lung growth (9, 10). There is increasing interest in how genetic susceptibility may alter the adverse impact of environmental insults on the lungs. One gene family of interest is GST (glutathione S-transferase). These genes code for a superfamily of enzymes involved in the detoxification of many noxious compounds in the body and are involved in regulation of oxidative stress and inflammatory pathways in the lungs (11). GST genes have been found to be a risk factor for COPD susceptibility (12), and our previous studies have shown evidence of interactions between GST genes and adverse environmental exposures for lung function deficits (13, 14).

The identification of individuals predisposed to the acceleration of age-related lung function decline may assist in selecting groups for targeted early preventive interventions. However, a comprehensive assessment of the impact of a wide range of adult risk factors and the potential interaction between childhood respiratory factors, genetic susceptibility, and adult factors on excess lung function decline is lacking. Also, studies have usually investigated the decline in prebronchodilator (pre-BD) spirometry, with few (15, 16) having investigated post-BD lung function decline, both without investigation of potential interactions. Investigating both outcomes may provide differing but complementary information. As distinct from pre-BD measures, post-BD lung function is a more accurate measurement of maximum lung function (after reversal of nonfixed bronchoconstriction) and the widely accepted measure used to define COPD (fixed airflow obstruction) (2). Post-BD forced expiratory volume in 1 second (FEV_1) decline may provide a better measure of pathological progression (e.g., airways remodeling), whereas changes in pre-BD FEV_1, although influenced by remodeling, can also be attributable to reversible factors (e.g., acute bronchoconstriction). In addition, most studies have focused only on the decline in FEV_1 (9, 17), although examining FEV_1, forced vital capacity (FVC), and FEV_1/FVC together would give more insights into obstructive and restrictive patterns and thereby potentially provide insights into the pathophysiology/mechanisms of risk factors associated with accelerated lung function decline.

Using data from the Tasmanian Longitudinal Health Study (TAHS), we aimed to investigate: *1*) the effects of multiple adult factors on lung function decline (FEV_1, FVC, and FEV_1/FVC) in middle age, with and without inhaled BD; and *2*) how childhood respiratory risk factors, low childhood lung function, and GST genes may interact with the effect of adult exposures.

Some of the results of this study have been previously reported in the form of an abstract (18).

Methods

Study Design and Population

The TAHS methodology has been reported in detail elsewhere (19). In brief, the TAHS began in 1968 when 8,583 Tasmanian school children who had been born in 1961 were enrolled in a respiratory health study, underwent a clinical examination and pre-BD spirometry, and their parents completed a questionnaire for the child. In 2002, the original 1968 cohort was retraced and resurveyed. A sample of respondents ($N = 1,389$) enriched for asthma and cough subsequently participated in a laboratory study between 2006 and 2008 (mean age, 45 yr), which included a detailed questionnaire plus pre- and post-BD spirometry. In 2012, surviving participants from the original cohort with contact details ($n = 6,128$, 71% of the original cohort) were invited to attend a clinical study. Between 2012 and 2016 (mean age, 53 yr), 3,609 participated (58.9% of those invited). Of those, 2,689 participants (74.5%) completed a questionnaire and performed pre- and post-BD spirometry, and 920 participants (25.4%) only completed a questionnaire. A total of 857 participants had post-BD

Supported by the National Health and Medical Research Council (NHMRC) of Australia under NHMRC project grant scheme (299901, 1021275) and NHMRC European collaborative grant scheme (1101313) as part of ALEC (Ageing Lungs in European Cohorts funded by the European Union's Horizon 2020 research and innovation program under grant agreement 633212); The University of Melbourne; Clifford Craig Medical Research Trust of Tasmania; the Victorian, Queensland, and Tasmanian Asthma Foundations; The Royal Hobart Hospital; Helen MacPherson Smith Trust; and GlaxoSmithKline. The funding agencies had no direct role in the conduct of the study; the collection, management, statistical analysis, or interpretation of the data; or the preparation or approval of the manuscript.

Author Contributions: Study concept and design: E.H.W., M.J.A., G.G.G., and S.C.D. Acquisition of data: E.H.W., J.A.B., P.S.T., S.M., and S.C.D. Analysis and interpretation of data: D.S.B., J.L.P., J.A.B., M.Q.B., G.B., A.J.L., M.A.R., S.M.A., B.R.T., G.S.H., D.P.J., L.D.K., J.-P.Z., A.M., J.G.-A., B.E., D.J., C.S., C.J.L., and S.C.D. Drafting of the manuscript: D.S.B., J.A.B., and S.C.D. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: D.S.B., J.A.B., and S.C.D. Obtained funding: E.H.W., M.J.A., S.M., and S.C.D.

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spirometry measured at two time points (45 and 53 yr) and made up the sample for this analysis (Figure 1).

The study was approved by the human ethics review committees of all relevant institutions. Written informed consent was obtained from all participants.

Lung Function Measurements

Lung function at both time points was measured with an EasyOne ultrasonic spirometer (ndd Medizintechnik AG). Participants were asked not to smoke for 4 to 6 hours before testing. FEV_1 and FVC were recorded as the best of three maneuvers that met American Thoracic Society/European Respiratory Society criteria for acceptable and repeatable spirometry (20). Spirometry was repeated 10 minutes after 300 μg of salbutamol administered via a spacer. The predicted normal and percent predicted values for individual parameters were derived from the Global Lung Initiative reference values (21).

Definition of Variables

Current asthma at age 45 or 53 years was defined by an affirmative response to the question "Have you ever had asthma?" plus asthma symptoms (including being woken up at night and morning symptoms), hospital admission or emergency department visits because of asthma, or use of asthma medication for breathing problems in the last 12 months. Current asthma was further classified into early onset (age $<$ 20 yr) or adult onset (age $\geq$ 20 yr) (22). Asthma status change from age 45 to 53 years was classified as persistent asthma (asthma at both time points), remitted asthma (asthma at age 45 yr but not 53 yr), incident asthma (asthma at 53 yr but not 45 yr), and no asthma at both time points.

Occupational exposures to vapors/gases/dusts/fumes (VGDF) and aromatic solvents were classified using the lifetime work history calendar that was collected from the participants at age 45 years and was categorized based on ALOHA plus Job Exposure Matrix (23).

Body mass index (BMI, kg/m^2) change between age 45 and 53 years was calculated by subtracting BMI at 45 years from BMI at 53 years.

Personal smoking status at age 45 years included three categories: never, past, or current. Persistent smokers during the follow-up included those who were current smokers at both age 45 and 53 years. Those who were current smokers at age 45 years but not at 53 years were classified as quitters during the follow-up. Pack-years were calculated using the smoking history provided.

Surrogates of exposure to traffic-related air pollution (TRAP) included residential distance from a major road ($<$200 m and $\geq$200 m) and mean annual nitrogen dioxide (NO_2) concentration estimated at the residential addresses at 45 years, using a validated satellite-based land-use regression model (24, 25) (*see* online supplement).

Childhood respiratory risk factors (childhood asthma, parental smoking, parental asthma, pneumonia, and chest illnesses) were defined using the questionnaire completed by participants' parents when the participants were aged 7 years (*see* online supplement). Low childhood lung function was defined as the lowest quartile of FEV_1 measured at age 7 years.

Genotyping of GSTM1 (non-null or null), GSTT1 (non-null or null), and GSTP1 (AA, AG, or GG) polymorphisms was performed from blood samples collected at age 45 years (*see* online supplement). Definitions of other variables are presented in the online supplement.

Statistical Analysis

Annual rates of change in absolute post-BD FEV_1, FVC, and FEV_1/FVC from age 45

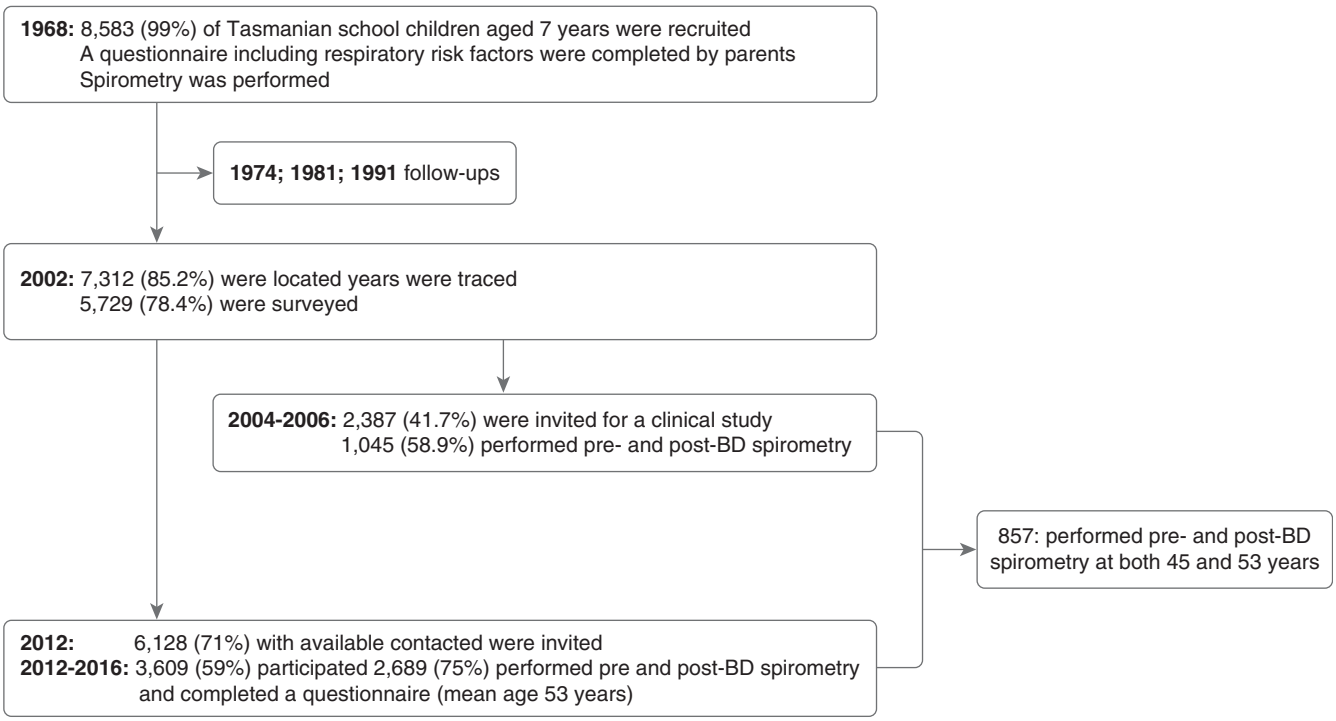

Figure 1. Flow chart of Tasmanian Longitudinal Health Study. BD = bronchodilator.

(baseline) to 53 years were calculated by taking the difference between the two time points and dividing by the follow-up period: ([value at baseline − value at follow-up]/follow-up time [yr]). We used multiple linear regression to investigate associations between factors in adulthood (current asthma, smoking status, atopy, lifetime occupational exposure, traffic pollution, and obesity) and annual rate of lung function decline. The excess lung function decline rate comparing the exposed group to the reference group for each risk factor was estimated from coefficients of multiple linear regression models. For each adult risk factor, we developed a directed acyclic graph model to select the minimum set of confounders to adjust for (Tables 1 and 2 footnotes; online supplement). Among commonly used proxies of TRAP, we had data to investigate the effect of NO_2 level and distance to major roads. The cutoff of 200 m was selected based on sharp decay in pollutant concentration means, that most TRAP components approach background levels at approximately 200 m away from a major road (26). Furthermore, our previous studies of TAHS showed strong effects of living <200 m from major roads on asthma, lung function, and allergic sensitization (13, 24, 27).

The possible interactions of adult factors with childhood respiratory risk factors (parental smoking, parental asthma, childhood asthma, pneumonia, and chest illnesses), low childhood lung function, and GST genes (GSTT1, GSTM1, and GSTP1) were tested by including an interaction term in the model and using likelihood ratio tests. Strata-specific estimates were reported if P for interaction was <0.1.

All analyses were performed using Stata 13.1 (Stata Corp).

Results

Characteristics of Participants

Lung function was measured in 857 participants at both age 45 (mean ± SD, 44.8 ± 0.8) and 53 (53.1 ± 0.7) years. Nearly half of participants (48.1%) were female (Table 3). The prevalence of current asthma was 22.6% at baseline and decreased to 17.5% at age 53 years. Of those with current asthma at baseline, 55% had persistent asthma and 45% had remitted at age 53 years. The prevalence of current smoking decreased from 23.7% to 14.1%. Of current smokers at baseline, 54% were persistent smokers, and 46% quit during the follow-up period. The prevalence of obesity (BMI > 30 kg/m^2) at age 45 years was 27.1%, and this increased to 32.1% at age 53 years.

During the mean follow-up of 8.3 (±0.9) years, the mean annual decline rates of post-BD spirometric measures were: FEV_1, 25.3 (95% confidence interval [CI], 23.3–27.3) ml/yr; FVC, 24.8 (95% CI, 22.2–27.4) ml/yr, and FEV_1/FVC, 0.14 (95% CI, 0.10–0.17) %/yr.

Effect of Baseline Exposures on Post-BD Lung Function Decline from Age 45 to 53 Years

The univariable associations between risk factors and lung function decline are presented in Tables E1 and E2 (online supplement). In the multiple model, having asthma, smoking, being exposed to VGDF, and living close to traffic at age 45 years were independently associated with accelerated decline in both post-BD FEV_1 and FEV_1/FVC (Table 1, Figure 2) from age 45 to 53 years. The effect of baseline asthma on post-BD FEV_1 and FEV_1/FVC decline was only significant for asthma of early onset (FEV_1, 7.2; 95% CI, 1.6–12.7 ml/yr, and FEV_1/FVC, 0.16; 95% CI, 0.07–0.26 %/yr) but not for asthma of adult onset (FEV_1, 1.6; 95% CI, −5.9 to 9.1 ml/yr, and FEV_1/FVC, 0.10; 95% CI, −0.02 to 0.23 %/yr). Smoking and increasing annual mean residential NO_2

Table 1. Adjusted associations between adulthood factors at baseline (45 yr) and post-BD lung function decline

Predictors	Excess Decline in Post-BD Lung Function		
	FEV_1 (*ml/yr*)	FVC (*ml/yr*)	FEV_1/FVC (*%/yr*)*
Current asthma (yes vs. no)	**5.3 (0.6 to 10)**†	2.3 (−4.1 to 8.7)	**0.14 (0.06 to 0.23)**‡
Smoking status			
Past (vs. never smoking)	−1.1 (−5.7 to 3.4)	−2.1 (−8.3 to 3.9)	0.01 (−0.06 to 0.09)
Current (vs. never smoking)	**14.4 (9.4 to 19.4)**‡	**9.3 (2.6 to 15.9)**§	**0.24 (0.15 to 0.32)**‡
Cumulative smoking (per 10 pack-years)	**1.9 (0.6 to 3.2)**§	1.6 (−0.2 to 3.4)	**0.03 (0.01 to 0.05)**†
Obesity	**−7.4 (−12 to −2.2)**§	−3.9 (−10 to 3.1)	**−0.09 (−0.18 to −0.003)**†
Occupational exposure			
Vapors/gas/dust/fumes	**8.3 (3.1 to 13.6)**§	5.6 (−0.4 to 11.6)	**0.11 (0.02 to 0.19)**†
Aromatic solvents	−1.0 (−5.6 to 3.5)	−2.6 (−8.7 to 3.4)	0.03 (−0.04 to 0.11)
Proxies for traffic air pollution			
Distance from main road < 200 m vs. ⩾200 m	**3.0 (1.1 to 4.9)**†	−0.7 (−6.7 to 5.2)	**0.08 (0.01 to 0.15)**†
NO_2 concentration (per IQR [2.2 ppb] increase)	0.8 (−1.1 to 2.6)	**1.9 (0.7 to 3.2)**†	−0.002 (−0.03 to 0.03)

Definition of abbreviations: BD = bronchodilator; BMI = body mass index; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; IQR = interquartile range; ppb = parts per billion; SES = socioeconomic status.

Data show the excess decline for the exposed group compared with the reference group for each factor. For example, those with current asthma had an excess FEV_1 decline of 5.3 ml/yr compared to those without current asthma. Negative values indicate a slower decline compared with the reference group. For asthma, models were adjusted for BMI/obesity status, types of heating/cooking, occupational exposure, passive smoking, active smoking, SES, sex, and traffic pollution. For smoking, models were adjusted for sex, SES, and childhood asthma. For obesity, models were adjusted for age, sex, smoking, and SES. For occupation exposure, models were adjusted for sex and SES. For traffic pollution, models were adjusted for age, sex, BMI/obesity, types of heating/cooking, occupational exposure, passive smoking, and active smoking. Bold typeface indicates statistical significance. Ranges are 95% confidence interval.

*Absolute values of change in the ratio (%) divided by the number of years between the lung function tests.

†$P < 0.05$.

‡$P < 0.001$.

§$P < 0.01$.

Table 2. Adjusted associations between longitudinal changes in asthma, smoking, and obesity status and post-BD lung function decline

Longitudinal Changes in Exposures between Two Time Points (45 and 53 yr)	Excess Decline in Post-BD Lung Function		
	FEV_1 (*ml/yr*)	FVC (*ml/yr*)	FEV_1/FVC (*%/yr*)*
Change in obesity status[†]			
Never obesity	Ref	Ref	Ref
Remitted obesity	**−18.9 (−29.0 to −8.9)**[‡]	**−16.9 (−30.4 to −3.5)**[§]	−0.12 (−0.29 to 0.05)
Incident obesity	**8.3 (1.8 to 14.9)**[§]	**17.3 (8.5 to 26.1)**[‡]	−0.13 (−0.25 to −0.02)[§]
Persistent obesity	−1.0 (−5.7 to 3.7)	4.1 (−2.2 to 10.5)	−0.08 (−0.16 to 0.001)
Change in smoking status[‖]			
Never-smokers	Ref	Ref	Ref
Persistent smokers	**20.3 (14.1 to 26.6)**[‡]	6.4 (−1.8 to 14.7)	**0.45 (0.34 to 0.56)**[‡]
Quitters	**8.3 (1.7 to 14.8)**[§]	**12.1 (3.3 to 20.9)**[§]	0.02 (−0.08 to 0.13)
Change in current asthma[¶]			
Noncurrent asthma	Ref	Ref	Ref
Persistent	**11.1 (5.0 to 17.2)****	5.8 (−2.3 to 14.1)	**0.25 (0.14 to 0.35)**[‡]
Remitted	0.2 (−6.3 to 6.7)	−0.3 (−9.3 to 8.7)	0.04 (−0.08 to 0.15)
Incident	**10.8 (2.0 to 19.6)**[§]	11.5 (−0.7 to 23.8)	0.06 (−0.09 to 0.21)

Definition of abbreviations: BD = bronchodilator; BMI = body mass index; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; Ref = reference group; SES = socioeconomic status.

Data show the excess decline for the exposed group compared to the reference group for each factor. Negative values indicate a slower decline compared to the reference group. Bold typeface indicates statistical significance. Ranges are 95% confidence interval.

*Absolute values of change in the ratio (%) divided by the number of years between the lung function tests.

[†]Models were adjusted for sex, SES, and childhood asthma.

[‡]$P < 0.001$.

[§]$P < 0.05$.

[‖]Models were adjusted for age, sex, smoking, and SES.

[¶]Models were adjusted for BMI/obesity status, types of heating/cooking, occupational exposure, passive smoking, active smoking, SES, sex, and traffic pollution.

**$P < 0.01$.

exposure at age 45 years were also associated with accelerated post-BD FVC decline.

Effect of Changes in Asthma, Smoking, and Obesity Status on Post-Bronchodilator Lung Function Decline from 45 to 53 Years

Both persistent smoking and quitting during the follow-up were associated with greater post-BD FEV_1 decline (excess rates: 20.3 and 8.3 ml/yr, respectively) (Table 2, Figure 3). Compared with those without asthma at both time points, participants with persistent asthma and incident asthma had a greater post-BD FEV_1 decline rate (excess rate: 11.1 and 10.8 ml/yr, respectively), and remitted asthma showed no increased post-BD FEV_1 decline (0.2 ml/yr). Similar findings were observed for post-BD FEV_1/FVC (Table 2). Compared with those who were never obese, those whose obesity reduced during follow-up had slower FEV_1 and FVC decline, and those who became obese had an accelerated decline (Table 2, Figure 3). Consistently, as a continuous measure, increase in BMI between the two time points was associated with accelerated decline in post-BD FEV_1 and FVC (excess rates: 3.7 and 5.3 ml/yr per kg/m^2 increase) but not in FEV_1/FVC.

Accentuation of the Effects of Adult Risk Factors by Low Childhood Lung Function, Early Life Exposures, and GST Genotypes

Significant interactions between low childhood lung function (especially for those in the lowest quartile) and both personal smoking at baseline (P for interaction = 0.06) and occupational exposure to VGDF (P for interaction = 0.04) were observed for post-BD FEV_1 decline. Although personal smoking was associated with accelerated decline in FEV_1 for all participants, the effect was greater for those in the lowest quartile of childhood lung function (excess rates: 23.3 vs. 11.3 ml/yr) (Figure 4, Table E3). On the other hand, exposure to VGDF was only associated with accelerated decline for those with lower childhood lung function (excess rates: 17.1 vs. 5.0 ml/yr) (Figure 4, Table E3).

We also found interactions between the effects of GSTM1 polymorphisms and occupational exposure to VGDF on both post-BD FEV_1 (P for interaction = 0.04) and FVC decline (P for interaction = 0.08). Accelerated decline in FEV_1 and FVC associated with VGDF exposure was only observed for participants who were carriers of the GSTM1 null genotype (Table E4).

There were also significant interactions between the effects of maternal smoking during childhood and personal smoking on declines in both post-BD FEV_1 (P for interaction = 0.08) and FVC (P for interaction = 0.04). Although current smoking was independently associated with accelerated post-BD FEV_1 and FVC decline, this association was much stronger for those who had mothers who smoked heavily, compared with mothers who were either nonsmokers or light smokers (Figure 4, Table E5).

Findings for Prebronchodilator Lung Function Decline

Associations between risk factors and pre-BD lung function decline were generally similar to those for post-BD lung function decline (Tables E6 and E7). The interaction between maternal smoking and personal smoking was also observed for pre-BD lung function decline. Some differences were also observed. Effects of occupational exposure to aromatic solvents were significant for

Table 3. Characteristics of participants studied at 45 years and 53 years ($N = 857$)

Characteristics	At 45 yr	At 53 yr
Age, years	44.8 ± 0.8	53.1 ± 0.7
Female	412 (48.1)	412 (48.1)
Current asthma	193 (22.6)	150 (17.5)
Early-onset asthma (<20 yr)	128 (15.0)	128 (15.0)
Late-onset asthma (≥20 yr)	65 (7.6)	65 (7.6)
Smoking status		
Never	391 (45.8)	391 (45.8)
Past	261 (30.5)	336 (39.5)
Current	202 (23.7)	120 (14.1)
Post-BD lung function		
FEV_1, L	3.48 ± 0.7	3.27 ± 0.7
FEV_1, % predicted	99.4 ± 12	100.2 ± 14
FVC, L	4.41 ± 0.9	4.20 ± 0.9
FVC, % predicted	100.9 ± 12	101.7 ± 12
FEV_1/FVC	0.79 ± 0.06	0.78 ± 0.06
BMI, kg/m^2	27.7 ± 5.0	28.7 ± 5.5
Obesity	232 (27.1)	275 (32.1)
Education levels		
Up to grade 12	323 (38.2)	323 (38.2)
Apprenticeship/diploma	314 (37.1)	314 (37.1)
Bachelor degrees or higher	209 (24.7)	209 (24.7)
GSTM1-null	394 (53)	394 (53)
GSTT1-null	124 (16.8)	124 (16.8)
GSTP1-val/val	96 (12.9)	96 (12.9)
Occupational exposures		
Vapors/gas/dust/fumes	338 (40.2)	
Aromatic solvents	243 (28.9)	

Definition of abbreviations: BD = bronchodilator; BMI = body mass index; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; GSTM1 = glutathione S-transferase Mu; GSTP1 = glutathione S-transferase Pi 1; GSTT1 = glutathione S-transferase Theta 1;SD = standard deviation. Data are presented as *n* (%) or mean ± SD.

pre-BD lung function decline but not for post BD decline (Table E6). Conversely, there was no evidence of interactions for smoking and occupational exposure to VGDF with low childhood lung function and GSTM1 genotype for pre-BD lung function decline, but only for post-BD lung function.

In addition to the associations between risk factors and lung function decline, we also observed a link between lung function decline rate and diffusing capacity for carbon monoxide (D_{LCO}) level at 53 years. D_{LCO} was lowest in the quartile of greatest FEV_1 decline (Table E8). This suggests a relationship between the decline in spirometry and emphysema.

Discussion

To our knowledge, this is the first study to investigate the interaction between childhood respiratory, genetic, and adult factors on the decline in post-BD lung function. We found that current smoking, current adult asthma, occupational exposures, and living close to major roads were associated with accelerated post-BD FEV_1 and FEV_1/FVC decline, a pattern suggestive of predisposition to airflow obstruction. Incident obesity and BMI gain were associated with both FEV_1 and FVC decline, a pattern suggestive of restrictive lung deficits. Importantly, we found susceptibility to the effects of adult risk factors was modified by specific childhood and genetic factors. In particular, accelerated lung function decline in current smokers and individuals exposed to occupational VGDF was greater for those with low lung function in childhood, a GSTM1 null genotype, or a mother who smoked. We found similar main effects for some but not all adult factors on pre-BD lung function decline. Our findings support the notion that an individual's susceptibility to accelerated post-BD lung function decline from respiratory hazards in adulthood may be programmed from childhood. These findings suggest that there are opportunities for interventions, both in childhood and adulthood, to prevent accelerated lung function decline and consequent fixed airflow obstruction.

Our findings support the hypothesis that reduced lung growth can predispose to subsequent steeper lung function decline (28). The observed synergistic effect between low childhood lung function and the common adult insults of smoking and occupational exposures is novel and of concern. Individuals with low childhood lung function who in later life either smoke and/or are exposed to occupational hazards may be the most vulnerable group for accelerated lung function decline. This synergy is particularly problematic because these individuals may already have lower levels of lung function by early adulthood (29), and, when coupled with accelerated lung function decline, they are at especially increased risk of developing COPD.

Previous studies (7, 30) have reported inconsistent findings for associations between adverse occupational exposures and lung function decline. The role of GST genes as an effect modifier for the effect of occupational exposures on lung function decline in this study suggests that genetic susceptibility might have contributed to lack of consistent findings. GST genes control enzymes involved in the regulation of airway oxidative stress through detoxification of reactive oxygen species (31), which may explain the underlying mechanism of the interaction found in our study. Screening for such genetic susceptibility could be used to educate carriers about their vulnerability to lung effects from high-risk occupations.

The adverse associations of active asthma and smoking with lung function decline have been reported (8, 32, 33). The excess post-BD lung function decline rates in relation to smoking in our study are consistent with a previous study by Pérez-Padilla and colleagues (15). We observed an excess decline rate of 14.4 ml/yr for FEV_1, which is similar to that of Pérez-Padilla and colleagues at 11.9 ml/yr (15). Our study additionally confirms the benefits of smoking cessation and having asthma remission (34). We found that lung function decline for those who quit smoking during the follow-up was reduced compared with persistent smokers, although still more rapid than never-smokers. The observed benefit of smoking cessation was independent of the adverse effect of coincident BMI increment (35). Similarly, although persistent asthma and incident asthma during the follow-up were associated with accelerated lung function decline, there was no effect for remitted asthma, when compared with

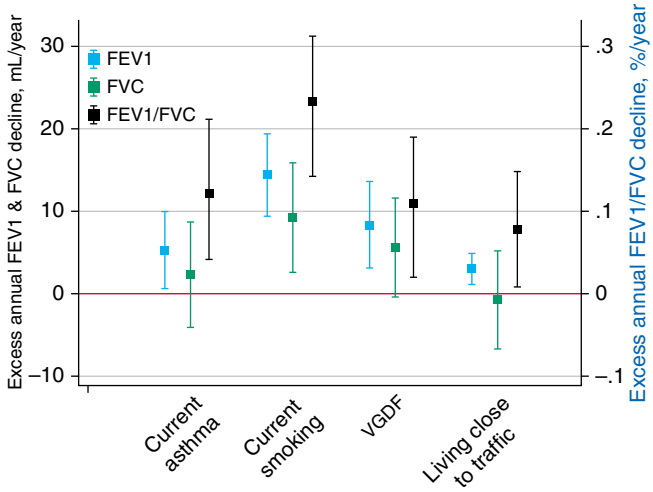

Figure 2. Associations between factors at baseline (45 yr) and post-bronchodilator forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), and FEV_1/FVC decline. Figure shows excess decline rate for current asthma (compared with no asthma), current smoking (compared with never-smoking), exposure to vapors/gases/dusts/fumes (VGDF), and traffic pollution (living <200 m from main roads). Negative values indicate a slower decline over follow-up. For asthma, models were adjusted for body mass index (BMI)/obesity status, types of heating/cooking, occupational exposure, passive smoking, active smoking, socioeconomic status (SES), sex, and traffic pollution. For smoking, models were adjusted for sex, SES, and childhood asthma. For occupation exposure, models were adjusted for sex and SES. For traffic pollution, models were adjusted for age, sex, BMI/obesity, types of heating/cooking, occupational exposure, passive smoking, and active smoking.

patients who never had asthma. These findings support the potential benefits from optimizing asthma control and smoking abstinence in preventing abnormally rapid lung function decline and, ultimately, COPD.

The adverse associations found between TRAP and accelerated lung function decline, both for living close to a major road and NO_2 exposure, support the proposition that air pollution exposure, even at the low levels found in Australia, may have serious implications for lung function decline. Previous reports of association between living close to traffic and lung function decline are inconsistent, with a US study (6) reporting an association, while a UK study did not (36). This discrepancy may result from the use of different cutoffs (100 and 150 m) for the exposure zone and varying traffic density in the two studies. For specific pollutants, the ESCAPE (European Study of Cohorts for Air Pollution Effects) study found no association between particulate matter and nitrogen oxides (NO_2, NOx) with lung function decline (37). More research is needed before informing public health initiatives, such as campaigns for replacement of diesel engines with electric ones for urban vehicles, which have so far had little emphasis or uptake in Australia.

Associations between BMI increase and incident obesity, and both FEV_1 and FVC decline but not FEV_1/FVC, were observed in this study. This is consistent with findings from the ECRHS (European Community Respiratory Health Survey) study, though FEV_1/FVC was not reported (35). Similarly, BMI increase was associated with FVC decline in a cohort of middle-aged Australians (38). In addition, an Italian study reported people who became obese over an 8-year follow-up had a greater decline in both FEV_1 and FVC, whereas those with persistent obesity had greater decline in FVC only (39). These findings provide further evidence that obesity is associated with a restrictive rather than obstructive lung function pattern. It is interesting that individuals who were obese at age 45 years but not at 53 years showed less decline in both FEV_1 and FVC than those who had never been obese, in contrast to an accelerated decline in those who became obese during follow-up. Thus, a reduction in obesity may have benefits for lung function outcomes in addition to other health outcomes. For example, bariatric surgery has been associated with a profound weight loss and improved lung function in obese people with or without asthma (40).

This article complements our previous publication (41) that reported the link between some childhood factors and lung function trajectories from childhood to adulthood. The comprehensive examination of effects of adult risk factors and their interactions with childhood and genetic factors on lung function decline, a critical phase of the lifetime lung function trajectory, in the present study provides additional insights into the development of COPD. Moreover, the current study sheds light on the potential mechanisms involved in the link between low childhood lung function and COPD in middle age (42).

At an individual level, the excess rates of lung function decline, particularly for the FEV_1/FVC ratio, in relation to risk factors examined in this study may be considered relatively small from a clinical viewpoint. However, these relatively small effects are still of significance, because a small deficit in lung function can impose a significant burden on the population, as shifting these risks can have a substantial impact on the lung function decline at a population level.

Our study adds to the existing literature by investigating lung function decline with and without inhaled BD, whereas previous studies mostly examined decline in pre-BD lung function. Post-BD FEV_1 decline provides a better measure of pathological progression (e.g., airways remodeling), whereas changes in pre-BD FEV_1, although influenced by remodeling, can also be attributable to reversible factors (e.g., acute bronchoconstriction). Moreover, pre-BD values are strongly influenced by the use of BD medication before scheduled spirometry testing, whereas post-BD values are less affected by inadequate washout periods. In the UPLIFT (Understanding Potential Long-term Impacts on Function with Tiotropium) study, the rates of FEV_1 and FVC decline were slightly higher for pre-BD than for post-BD measures among subjects with mild COPD (43). In contrast, the rates of decline were significantly greater for post-BD measures than for pre-BD measures among those with moderate to severe COPD (44). The underlying reason for the discrepancy between pre-BD and post-BD decline rates is not clear. The variability of BD responsiveness over time and by age, degree of baseline airflow obstruction, and smoking and asthma status adds more complexity, which may not be captured by pre-BD measures alone (44, 45). Consequently, both pre-BD and post-BD decline should be jointly considered, particularly when assessing the effect of risk factors on lung function decline."

The notable strength of this study is its longitudinal follow-up over 6 decades,

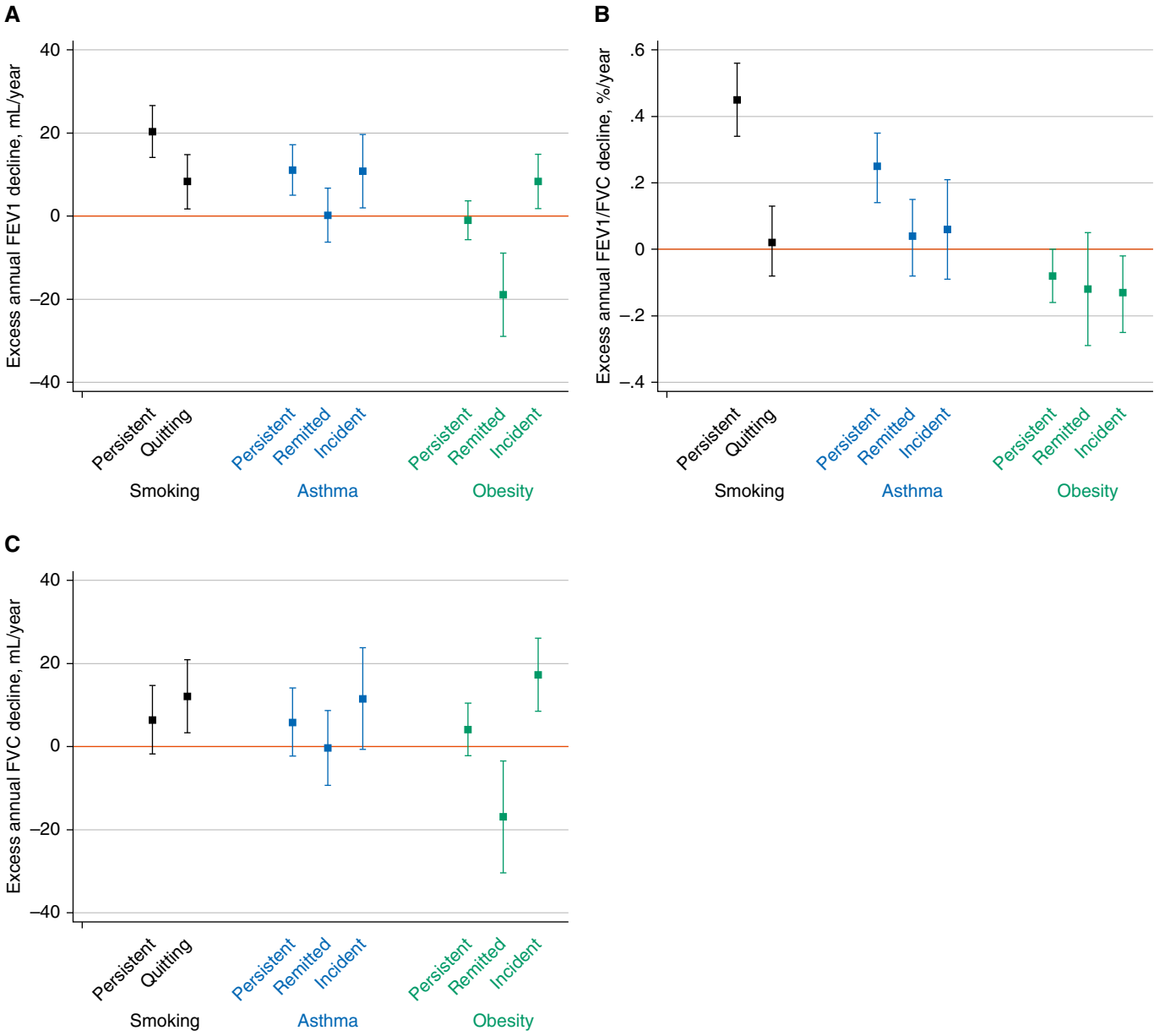

Figure 3. Associations between changes in exposures between 45 and 53 years and post-bronchodilator (*A*) forced expiratory volume in 1 second (FEV_1), (*B*) FEV_1/forced vital capacity (FVC), and (*C*) FVC decline. Figure shows excess decline rate for changes in smoking status (compared with never smoking), asthma status (compared with no asthma), and obesity status (compared with never-obesity) between 45 and 53 years. Negative values indicate a slower decline over follow-up. For asthma, models were adjusted for body mass index/obesity status, types of heating/cooking, occupational exposure, passive smoking, active smoking, socioeconomic status (SES), sex, and traffic pollution. For smoking, models were adjusted for sex, SES, and childhood asthma. For obesity, models were adjusted for age, sex, smoking, and SES.

which allowed us to examine the modifying effect of potential childhood factors collected in childhood, rather than retrospectively collected based on adult recall. Another strength is the sufficiently large sample size, which permitted a comprehensive analysis of interactions. Although several studies have investigated decline in FEV_1 only, we considered decline in FEV_1, FVC, and FEV_1/FVC together. Including these three parameters allowed us to differentiate between patterns of the decline as either obstructive or restrictive.

Our study also has some limitations. First, by design, the participant sample at baseline for this analysis (age 45 yr) was enriched for those with asthma and cough, which might affect the generalizability of our results to some degree; this enrichment is unlikely to have affected the associations found, and adding sampling weights to analytical models did not significantly change our findings. Second, in this study, the same protocols, calibration procedures, and spirometers were used at both follow-ups (45 and 53 yr). However, some subjects were tested by different technicians at 45 and 53 years, a limitation that we attempted to overcome by uniform protocols and rigorous training of the technicians. Third,

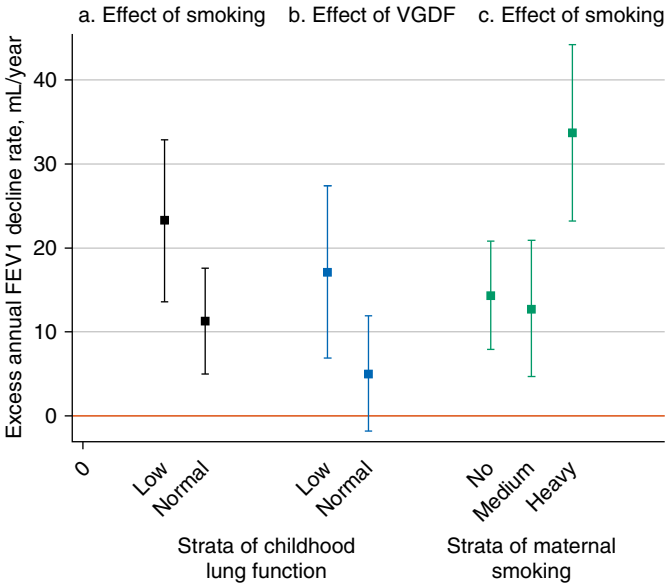

Figure 4. Interactions of smoking and occupational vapors/gases/dusts/fumes (VGDF) with childhood lung function and maternal smoking. Figure shows excess post-bronchodilator forced expiratory volume in 1 second (FEV_1) decline rate in current smoking compared with (*A* and *C*) never smoking, and (*B*) occupational exposure to VGDF compared with nonexposure stratified by childhood lung function (lowest vs. other quartiles) and maternal smoking. Negative values indicate a slower decline over follow-up.

as we performed multiple tests for interactions, some results may be spurious findings, although the stratified results were consistent and biologically plausible, suggesting findings of interactions were unlikely to be by chance. In addition, in this analysis, we used a targeted approach to focus on GST genes, given the increasing interest in the role of oxidative stress in lung diseases and our previous studies showing interactions between GST genes and adverse environmental exposures (13, 14). However, the role of other genes, such as those known to be associated with oxidative stress management and with COPD, should be further investigated. Furthermore, there is a lack of consensus on a "gold standard" for the BD dose used in BD reversibility testing. Although a dose of 300 μg of salbutamol was administered in the TAHS, a dose of 400 μg of salbutamol is also recommended by some (35). Thus, the maximum lung function effects might have been underestimated, as nondifferential error pushes estimates toward null, and therefore our positive findings are unlikely to be biased.

Like many epidemiological studies, we were unfortunately unable to verify self-reported smoking status by objective measures in TAHS. This is a limitation of this study, as self-reported information tends to underestimate smoking prevalence (46). However, in general population-based studies like TAHS, misclassification is likely to be small (47). One concern within this longitudinal study is the potential for selective attrition to have biased the results. It should be noted that of those who have died, the main causes of death were external injury (56.1%), cancer (17.9%), and circulatory diseases (9.8%). Only 1.1% of participants died from respiratory conditions. Because death was not primarily related to the outcome, it would be unlikely to significantly affect associations found in this study. Last, to more precisely assess lung function decline rates, multiple measurements at appropriately spaced intervals would be ideal. Having only two time points limited our ability to capture detailed changes in the rate of lung function during the follow-up.

Conclusions

Our study strengthens the evidence that adult factors, including asthma, smoking, occupational exposures, and traffic pollution, are determinants of accelerated airflow obstruction in middle age, whereas obesity is associated with an accelerated restrictive pattern. Notably, we provide novel evidence that susceptibility to accelerated post-BD FEV_1 decline due to these insults in adulthood may be enhanced by childhood and genetic factors, such as low childhood lung function, GSTM1 null genotype, and maternal smoking. We emphasize the importance of smoking abstinence and occupational risk reduction/protection, especially for individuals with preexisting low lung function from childhood risk factors and GSTM1 null genotype, to minimize harm from accelerated lung function decline in mid-adult life. Our findings also highlight that investigating both pre- and post-BD lung function decline is informative for understanding potential mechanisms of risk factors. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Acknowledgment: The authors thank the TAHS study participants and previous investigators. They also thank Professor Mark Jenkins, Ph.D., Centre for Epidemiology and Biostatistics, The University of Melbourne, Victoria, a TAHS investigator, but not a co-author of this manuscript, for his assistance with obtaining funds and data collection. We also acknowledge all the respiratory scientists who collected data in the lung function laboratories of Tasmania, Victoria, Queensland, and New South Wales, and the research interviewers, data entry operators, and research officers. Finally, we thank the Archives Office of Tasmania for providing data from the 1968 TAHS questionnaires.

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