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Authors

Zeng, Siyang
Dunn, Michelle
Gold, Warren M
et al.

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Remote exposure to secondhand tobacco smoke is associated with lower exercise capacity through effects on oxygen pulse, a proxy of cardiac stroke volume

Siyang Zeng ,^{1,2} Michelle Dunn,² Warren M Gold,³ Jorge R Kizer,^{3,4,5} Mehrdad Arjomandi ^{2,3}

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ABSTRACT

Background Past exposure to secondhand tobacco smoke (SHS) is associated with exercise limitation. Pulmonary factors including air trapping contribute to this limitation but the contribution of cardiovascular factors is unclear.

Objective To determine the contribution of cardiovascular mechanisms to SHS-associated exercise limitation.

Methods We examined the cardiovascular responses to maximum-effort exercise in 245 never-smokers with remote, prolonged occupational exposure to SHS and no known history of cardiovascular disease. We estimated the contribution of oxygen-pulse (proxy for cardiac stroke volume) and changes in systolic blood pressures (SBP), diastolic blood pressures and heart rate (HR) towards exercise capacity, and examined whether the association of SHS with exercise capacity was mediated through these variables.

Results At peak exercise (highest workload completed ($\text{Watts}_{\text{Peak}}$)=156±46 watts (135±33 %predicted)), oxygen consumption and oxygen-pulse ($\text{O}_2\text{-Pulse}_{\text{Peak}}$) were 1557±476 mL/min (100±24 %predicted) and 11.0±3.0 mL/beat (116±25 %predicted), respectively, with 29% and 3% participants not achieving their predicted normal range. Oxygen saturation at peak exercise was 98%±1% and remained >93% in all participants. Sixty-six per cent showed hypertensive response to exercise. In models adjusted for covariates, $\text{Watts}_{\text{Peak}}$ was associated directly with $\text{O}_2\text{-Pulse}_{\text{Peak}}$, HR_{Peak} and SBP_{Peak} and inversely with SHS, air trapping (residual volume/total lung capacity) and rise of SBP over workload (all $p<0.01$). Moreover, SHS exposure association with $\text{Watts}_{\text{Peak}}$ was substantially (41%) mediated through its effect on $\text{O}_2\text{-Pulse}_{\text{Peak}}$ ($p=0.038$). Although not statistically significant, a considerable proportion (36%) of air trapping effect on $\text{Watts}_{\text{Peak}}$ seemed to be mediated through $\text{O}_2\text{-Pulse}_{\text{Peak}}$ ($p=0.078$). The likelihood of having baseline respiratory symptoms (modified Medical Research Council score ≥1) was associated with steeper rise in SBP over workload ($p<0.01$).

Conclusion In a never-smoker population with remote exposure to SHS, abnormal escalation of blood pressure and an SHS-associated reduction in cardiac output contributed to lower exercise capacity.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Prolonged past exposure to secondhand tobacco smoke is associated with exercise limitation. Pulmonary factors including air trapping contribute to this limitation but the contribution of cardiovascular factors is unclear, as is the interaction between pulmonary and cardiovascular systems in this setting.

WHAT THIS STUDY ADDS

⇒ Healthy never-smokers with history of remote exposure to secondhand tobacco smoke have an abnormal cardiovascular response to exercise, which is characterised by a stroke volume and thus an exercise capacity that are reduced proportional to their years of exposure to secondhand tobacco smoke.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE AND/OR POLICY

⇒ The abnormal cardiovascular response to exercise in this population reveals the presence of an occult or subclinical pathology that impairs the cardiopulmonary functional reserve and reduces the efficiency of body's oxygen delivery machinery, which could be disadvantageous during the times of increased cardiopulmonary output demands as in physiological distress or disease.

INTRODUCTION

Secondhand tobacco smoke (SHS) remains a major public health problem.^{1,2} Although SHS exposure among non-smokers in the USA has declined from 88% in 1988 to 25% in 2014, the rate of decline has plateaued with one in four non-smokers, including 14 million children, continuing to be exposed to SHS annually between 2011 and 2014.³ The consequences of such substantial continued exposure may now be more manifest as the generations that endured the highest levels of SHS exposure grow older. In particular, advancing age could aggravate or unmask SHS-related



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For numbered affiliations see end of article.

Correspondence to

Dr Mehrdad Arjomandi; mehrdad.arjomandi@ucsf.edu



health problems that may have been previously too subtle to be recognised.

Although immediate health effects of exposure to SHS have been studied,^{4–9} its long-term consequences, particularly the effect of remote exposures, have been more difficult to examine in part because of challenges with exposure assessment. Never-smoking flight crews who worked on commercial aircrafts before the enactment of the smoking ban were exposed to heavy SHS in aircraft cabin for many years, in a range similar to the nicotine exposure burden experienced by ‘light’ smokers.^{10,11} The regularity of this intense exposure in the cabin work environment lends itself to relatively accurate SHS exposure quantification through employment history.¹² This makes the exposed flight crews a unique population in which the long-term health effects of previous exposure to SHS can be examined as a form of ‘natural’ experiment that is also generalisable to other SHS-exposed populations.

In previous studies of never-smoking flight crews with a history of remote but prolonged exposure to SHS in aircraft cabins, we examined the pulmonary health effects of long-term exposure to SHS. These studies showed an association of adverse pulmonary outcome measures with the number of years during which flight crews were exposed to SHS in aircraft cabins.^{12–14} While this never-smoking SHS-exposed cohort had no evidence of spirometric chronic obstructive pulmonary disease (COPD) (a preserved ratio of forced expiratory volume in 1 s to forced vital capacity), they had abnormal lung function measures that were suggestive of presence of an occult early/mild obstructive lung disease.¹⁴ In the current study, we wished to examine the cardiovascular health effects of remote but prolonged exposure to SHS in this never-smoking cohort with evidence of early obstructive lung disease. We hypothesised that in addition to impacting pulmonary mechanisms (eg, air trapping), prolonged exposure to SHS contributes to exercise limitation through its adverse cardiovascular health effects. To evaluate this hypothesis, we analysed the cohort’s cardiovascular response to maximum effort cardiopulmonary exercise testing.

METHODS

Study overview

This was a prespecified analysis of data collected as part of the Secondhand Smoke Respiratory Health Study, an observational cohort study of non-smoking participants with a range of occupational SHS exposure, as previously described.^{12–14} Briefly, between July 2007 and July 2015, we recruited US airline flight crewmembers with a history of occupational exposure to SHS, along with non-smoker controls without such occupational exposure, who were participating in a larger study of cardiopulmonary health effects of prolonged remote exposure to SHS.¹⁴ The participants were characterised by respiratory symptom questionnaires, full pulmonary function testing and a maximum effort cardiopulmonary exercise

testing (CPET). We used the data from this cohort to perform a prespecified analysis to determine the associations among exercise capacity (highest workload completed (Watts_{Peak} in Watts), volume of oxygen uptake at peak exercise (VO_{2Peak} in L/min) and cumulative work achieved (Work_{Total} in Watts-Minutes)), cardiovascular responses to maximum effort CPET (oxygen-pulse (O₂-Pulse; a proxy for cardiac stroke volume), systolic and diastolic blood pressures (SBP and DBP) and heart rate (HR)), years of airline employment during which the participants worked in smoky cabin (cabin SHS exposure) and their interactions with each other as well as with air trapping (ratios of residual volume, or functional residual capacity, to total lung capacity; RV/TLC or FRC/TLC), which we had previously shown to be associated with exercise capacity (Watts_{Peak} and VO_{2Peak}).

Study population

The Secondhand Smoke Respiratory Health Study recruited the USA airline flight crewmembers as part of an investigation of the potential adverse health effects of the cabin environment on those employed before and after introduction of the ban on smoking in US commercial aircraft. Crewmembers were eligible to participate in the study if they had worked ≥ 5 years in aircraft. A referent group of ‘sea-level’ participants who lived in the San Francisco Bay area and had never been employed as airline crewmembers was also recruited. All participants were non-smokers defined by never-smoking or, in ever smokers, a cumulative history of smoking < 20 pack-years and no smoking for ≥ 20 years prior to enrolment. Participants with known history of pulmonary disease (such as asthma or COPD) or cardiovascular disease (such as coronary artery disease or heart failure) were excluded. Participants with known history of hypertension were included if their blood pressure was medically controlled as defined by SBP ≤ 145 and DBP ≤ 90 mm Hg at the time of visit. Overall, out of the 283 participants who underwent CPET, 245 individuals were included in this analysis after such exclusions (figure 1).¹⁴

Institutional Review Board approval

The University of California San Francisco (UCSF) Institutional Review Board (IRB) and the San Francisco Veterans Affairs (VA) Medical Center Committee on Research and Development approved the study protocols. Written IRB-approved informed consent and Health Insurance Portability and Accountability Act were obtained from all study participants. All participants received monetary compensation for their participation in the study.

Patient and public involvement

Patients or the public were not involved in the design, conduct, reporting or dissemination plans of our research. However, the participants did act as a referral

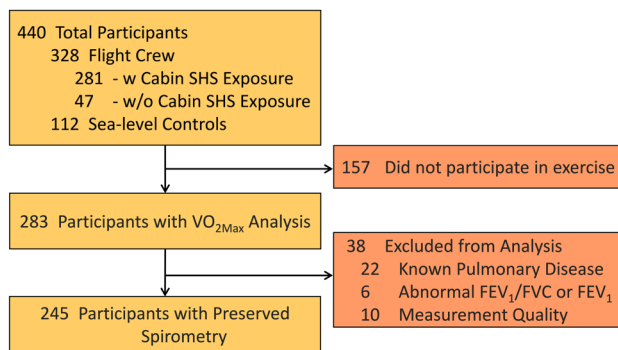


Figure 1 Participants flow through the study. BMI, body mass index; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; PFT, pulmonary function test; SHS, secondhand tobacco smoke; VO_{2Max}, volume of maximum oxygen uptake.

source and referred other interested potential people to participate in our study, and in that sense participated in dissemination of the study.

SHS exposure characterisation

SHS exposure was characterised by a questionnaire developed by the UCSF Flight Attendant Medical Research Institute (FAMRI) Center of Excellence,¹⁵ and modified to acquire information on airline-related occupational history (UCSF FAMRI SHS Questionnaire), as detailed in the online supplemental appendix and described previously.^{12 13}

Pulmonary function and cardiopulmonary exercise testing

Details of pulmonary function and maximum effort cardiopulmonary function testings are available in the online supplemental appendix and have been previously.^{12 14}

Respiratory symptom scoring

Respiratory symptoms were assessed using modified Medical Research Council (mMRC) Dyspnoea Scale¹⁶ and another self-reported questionnaire (UCSF FAMRI SHS Questionnaire) that elicited symptoms of dyspnoea, cough and participants' perception of a decreased level of exertion compared with peers over the year preceding enrolment.¹⁵ A dichotomous indicator of respiratory symptoms was defined by mMRC ≥ 1 or report of at least one respiratory symptom on the UCSF FAMRI SHS Questionnaire. A dichotomous cause of exercise cessation (dyspnoea vs fatigue or effort; Dyspnoea_{Peak}) was determined based on the highest score reported by the participants at the end of the maximum effort exercise testing using the modified Borg Rating of Perceived Exertion (Borg), with the Category-Ratio Scale anchored at number 10 (CR10).¹⁷

Data analysis

Per cent predicted as well as lower and upper limits of normal (LLN and ULN) values for measures of spirometry and lung volumes at rest and cardiopulmonary responses to exercise were calculated using Global Lung Function Initiative, Quanjer *et al*, and Wasserman *et al* predicted formulas, respectively.^{18–20} American Thoracic Society guidelines were also used for assessment of normal ranges of cardiopulmonary exercise indices.²¹

Distributions of participants' characteristics, pulmonary function, cardiopulmonary exercise and SHS exposure quantification variables were examined. Changes in HR, SBP, DBP and O₂-Pulse with respect to the workload were approximated by estimating the slopes from linear regression modelling of those measures (HR, SBP, DBP and O₂-Pulse) over workload at each stage. Peak cardiopulmonary exercise variables were estimated using the last 30 s average values obtained during the highest stage of the exercise test as described above. Cumulative work achieved throughout the exercise (Work_{Total}), or the area under the curve of workload in Watts versus time in minutes, was computed as the sum of the product of watts completed and time spent at each stage in the unit of Watts-Minute. A comparison of the distributions was performed using an unpaired t-test for each continuous variable or a χ^2 test for each binary or categorical variable.

Associations between exercise capacity (Watts_{Peak}, Work_{Total} or VO_{2Peak}, as dependent variables) and each of the cardiovascular outputs (including SBP, DBP and O₂-Pulse, as independent variables) were examined in multivariable linear regression models with adjustment for covariates (age, sex, height and body mass index (BMI) unless noted otherwise). Because O₂-Pulse (proxy for stroke volume) estimates were calculated using VO₂ and HR, the associations and mediation analyses of O₂-Pulse was only examined with Watts_{Peak} and Work_{Total} measures of exercise capacity and not with VO_{2Peak} to prevent bias from 'mathematical coupling'.²²

Similarly, associations between presence of respiratory symptoms (mMRC or UCSF FAMRI SHS Questionnaire, as dependent variables) and each of the cardiovascular outputs (as independent variables) were examined in multivariable logistic regression models with adjustment for covariates. The respective baseline variable was also adjusted whenever a slope variable was used in a model. Additionally, associations between each of the cardiovascular outputs (SBP, DBP and O₂-Pulse) and baseline air trapping (FRC/TLC or RV/TLC) as a pulmonary factor affecting exercise capacity and cardiovascular outputs,^{23–26} and SHS exposure were examined using linear regression models.

To investigate potential confounding effects of respiratory symptoms on the association of exercise capacity with cardiovascular outputs, we also performed multivariable regression modelling of exercise capacity (work)

versus relevant cardiovascular outputs along with respiratory symptoms to determine the adjusted contributions of these variables to exercise capacity.

To assess whether associations between exercise capacity and SHS exposure or air trapping (FRC/TLC or RV/TLC) were potentially mediated through cardiovascular outputs, we performed mediation analyses with exercise capacity (dependent variable), SHS exposure or air trapping (independent variable) and cardiovascular outputs (mediator variables), with inclusion of covariates using the 'mediation' package in R.²⁷ Absolute proportion of mediated effects with corresponding p values were reported.

For each analysis, the total number of participants who had complete set of data for that analysis was reported along with the results from the regression modelling or mediation analysis. Statistical significance was defined as a P-value <0.05.

RESULTS

Participant characteristics and response to exercise

The characteristics of the 245 individuals included in this analysis are shown in table 1. All participants reported ceasing exercise due to dyspnoea or leg fatigue. When pressed to identify a single cause for ceasing exercise, 117 (48%) identified dyspnoea as opposed to fatigue or effort as the main cause (Dyspnoea_{Peak}) (table 2).

The average volume of oxygen consumption at peak exercise (VO_{2Peak}) was 1557±476 mL/min (100±24 %predicted) with 71 (29%) having a VO_{2Peak} <84 %predicted, a presumed threshold for abnormal results. This VO_{2Peak} was achieved at a peak workload of 156±46 watts (135±33 %predicted). The ratio of oxyhaemoglobin to total haemoglobin (oxygen saturation or SpO_{2Peak}) at peak exercise was 98%±1% with nearly all participants but one having a SpO_{2Peak} of >93%. The pulmonary response to exercise was remarkable for a peak-exercise minute ventilation (V_{EPeak}) of 57.0±17.0 L/min (50±12 %predicted) with only 12 (5%) exceeding the 70% threshold for inappropriate ventilatory response to maximum effort exercise. The peak-exercise respiratory rate (RR_{Peak}) remained below the 60 breaths/min threshold in all but one participant (table 2). All participants reached their anaerobic threshold (VO_{2AT}) as determined by V slope method. Furthermore, ventilatory efficiency (V_E/VCO₂) at peak exercise was 30.7±3.8 (108±12 %predicted) with lowest V_E/VCO₂ at 29.4±3.4 (103±11 %predicted) (table 2).

None of the participants reported any chest pain, chest tightness, lightheadedness or dizziness during the CPET. None had any clinically significant ECG changes or arrhythmia besides occasional premature ventricular contractions that did not increase in frequency with exercise testing. Nevertheless, 66% of the participants (149 out of 226) showed a hypertensive response to exercise by at least one established criterion. The heart rate at peak exercise was 142±18

beat/min (85±10 %predicted). Oxygen-pulse at peak exercise (O₂-Pulse_{Peak}) was 11.0±3.0 mL/beat (116±25 %predicted), with 8 (3.3%) participants not achieving their 80% predicted values (a presumed threshold for abnormal results). Further details of the exercise test are discussed in the online supplemental appendix.

Association of exercise capacity with cardiovascular response measures, air trapping and SHS exposure

In multivariable models that included each (single) cardiopulmonary exercise testing (CPET) output separately as a predictor along with age, sex, height and BMI as covariates, workload (as measured by Watt_{Peak} or VO_{2Peak}) and cumulative work (as measured by Watt-Minute) were positively associated with the peak of heart rate and systolic blood pressure during exercise (HR_{Peak} and SBP_{Peak}). However, workload and cumulative work were negatively associated with the rate of increase in SBP, DBP and HR (HR_{Slope}, SBP_{Slope} and DBP_{Slope}) (all p<0.05), with faster rise of these indices being associated with lower workload or cumulative work the participants could achieve (table 3). Similarly, workload (Watt_{Peak}) and cumulative work (Watt-Minute) were associated positively with O₂-Pulse_{Peak} but negatively with O₂-Pulse_{Slope}. Moreover, Watt_{Peak}, VO_{2Peak} and Watt-Minute were positively associated with respiratory rate, tidal volume and minute ventilation at peak exercise (RR_{Peak}, V_{TPeak} and V_{EPeak}) and negatively with a lung function measure of air trapping (RV/TLC) (all p<0.05) (table 3).

Workload (Watt_{Peak} and VO_{2Peak}) was also negatively associated with years of exposure to cabin SHS (both p<0.05), but was not significantly associated with non-cabin SHS exposure including childhood and adulthood home exposures (table 3).

Association of respiratory symptoms with cardiopulmonary response measures

The association of respiratory symptoms with exercise measures were examined by determining the likelihood of having respiratory symptoms at baseline (mMRC ≥1 or any respiratory symptoms by FAMRI SHS questionnaire) or reporting dyspnoea at peak exercise as the main cause of exercise cessation (reporting higher dyspnoea score on Borg Dyspnoea Scale (Dyspnoea_{Peak})). As shown in table 4, baseline respiratory symptoms (as measured by mMRC Dyspnoea Scale) were negatively associated with workload (Watt_{Peak} or VO_{2Peak}) and cumulative work (Watt-Minute) achieved. Respiratory symptoms at baseline (as measured by FAMRI questionnaire) and at peak exercise (as measured by modified Borg Dyspnoea Scale) were not significantly associated with exercise capacity.

Overall, only a few CPET outputs were associated with respiratory symptoms. Among cardiovascular outputs, the likelihood of having an mMRC ≥1 was associated with faster rise in SBP (SBP_{Slope}) and with lower HR at peak exercise (HR_{Peak}). On the other hand, the likelihood of stopping exercise due to dyspnoea as measured

Table 1 Participant characteristics

Participant characteristics	All (N=245)	Unexposed (N=106)	Exposed (N=139)	P value
Demographics and anthropometrics				
Age (years)	53.8±11.3	47.1±11.8	58.9±7.7	<0.001
Female sex (n (%))	213 (86.9)	25 (23.6)	7 (5.0)	<0.001
Height (cm)	166.3±7.1	167.6±8.6	165.4±5.5	0.046
Weight (kg)	66.3±11.5	66.9±12.3	65.8±11.0	0.754
BMI (kg/m ²)	23.9±3.6	23.7±3.3	24.1±3.9	0.733
Haemoglobin (g/dL)	14.2±1.3	14.3±1.4	14.1±1.2	0.640
Smoking history (pack-years) (min–max)	0–3	0–3	0–1	0.811
History of hypertension (n (%))	11 (4.5)	5 (4.7)	6 (4.3)	0.989
SHS exposure				
Ever cabin SHS exposure (n (%))	139 (56.7)	0 (0)	139 (100)	<0.001
Cabin SHS exposure among exposed (years)	9.3±10.7	0±0	16.6±9.1	<0.001
Time since last cabin SHS exposure (years)	17.3±6.9	--	17.3±6.9	NA
Any form of non-cabin SHS exposure (n (%))	245 (100)	106 (100)	139 (100)	<0.001
Childhood home SHS exposure (n (%))	116 (47.3)	41 (38.7)	75 (54.0)	0.059
Adult home SHS exposure (n (%))	59 (24.1)	17 (16.0)	42 (30.2)	0.036
Non-airline occupational SHS exposure (n (%))	72 (29.4)	23 (21.7)	49 (35.3)	0.069
Other SHS exposure (n (%))	111 (45.3)	46 (43.4)	65 (46.8)	0.872
Symptoms				
mMRC Dyspnoea Scale ≥1 (n (%))	25 (10.2)	11 (10.4)	14 (10.1)	0.997
Participants with any respiratory symptoms (n (%))	112 (45.7)	47 (44.3)	65 (46.8)	0.931
Participants ever experiencing shortness of breath (n (%))	29 (11.8)	6 (5.7)	23 (16.5)	0.032
Participants with cough ≥2 episodes/year (n (%))	103 (42.0)	45 (42.5)	58 (41.7)	0.994
Participants with less activity than peers (n (%))	5 (2.0)	1 (0.9)	4 (2.9)	0.570
Pulmonary function tests				
FEV ₁ (% predicted)	103±12	104±12	102±13	0.194
FVC (% predicted)	107±13	109±14	106±13	0.300
FEV ₁ /FVC	77±5	78±5	76±5	0.003
FEV ₁ /FVC (% predicted)	95±6	96±6	95±6	0.784
FEF _{25–75} (% predicted)	94±25	95±23	94±27	0.915
FEF ₇₅ (% predicted)	112±44	112±42	112±45	0.999
D _{LCO} adjusted for Hgb (% predicted)	81±11	82±10	79±11	0.169
D _L /V _A adjusted for Hgb (% predicted)	123±16	121±18	125±15	0.190
Alveolar volume (V _A) (L) (% predicted)	95±12	97±13	94±11	0.133
TLC (% predicted)	103±11	104±11	103±11	0.888
RV (% predicted)	96±18	94±19	97±17	0.470
RV/TLC	33±7	30±7	36±6	<0.001
RV/TLC (% predicted)	90±13	88±14	91±11	0.165
FRC (% predicted)	103±20	103±20	103±20	0.999
FRC/TLC	53±7	52±7	54±8	0.341
FRC/TLC (% predicted)	99±13	99±13	98±14	0.966

Continued



Table 1 Continued

Participant characteristics	All (N=245)	Unexposed (N=106)	Exposed (N=139)	P value
Demographics, secondhand smoke (SHS) exposure, symptoms and lung function in participants with preserved spirometry that underwent exercise testing. Other SHS exposure was defined as non-aircraft cabin SHS exposure outside the work or home environment such as in recreational public places. Data are presented as mean±SD or number of participants with positive value for the variable (n) out of the total number of participants (N) and percentage of participants (%). Reference equations: per cent predicted of normal values of spirometry, diffusing capacity and lung volumes were calculated using Global Lung Function Initiative, Crapo <i>et al</i> and Quanjer <i>et al</i> predicted formulas, respectively. ^{18–20 45}				
BMI, body mass index; DcoSB, single-breath diffusing capacity of carbon monoxide; FEF ₇₅ , maximum airflow at low-lung volume; FEF _{25–75} , maximum airflow at mid-lung volume; FEV ₁ , forced expiratory volume in 1 s; FRC, functional residual capacity; FVC, forced vital capacity; Hgb, haemoglobin; mMRC, modified medical research council; RV, residual volume; TLC, total lung capacity.				

by modified Borg Dyspnoea Scale was associated with a higher DBP at peak exercise (DBP_{Peak}). Among pulmonary outputs, the likelihood of having an mMRC ≥1 was associated with lower RR and V_E at peak exercise (RR_{Peak} and V_{EPeak}), and lower anaerobic threshold (VO_{2AT}). Furthermore, baseline respiratory symptoms were significantly associated with FRC/TLC with more air trapping being associated with higher likelihood of having respiratory symptoms at baseline (RV/TLC association was marginally significant; p≤0.079).

Association of cardiovascular response measures with SHS exposure

Among the cardiovascular predictors of exercise capacity, O₂-Pulse_{Peak} was negatively associated with years of exposure to cabin SHS, showing a parameter estimate of -0.032±0.015 (p=0.040), which indicates a decrease in O₂-Pulse_{Peak} of 0.32 mL/beat for every 10 years increase in exposure to cabin SHS (online supplemental table S1). Consistently, the rate of increase in heart rate (HR_{Slope}) was directly associated with years of exposure to cabin SHS (online supplemental table S1). Furthermore, mediation analysis showed that a substantial fraction of cabin SHS exposure association with exercise capacity (Watt_{Peak}) was mediated through the SHS relationship with O₂-Pulse (41%; p=0.038) (table 5). Although not significant, cabin SHS association with cumulative work (Watt-Minute) also seemed to be mediated through O₂-Pulse (74%; p=0.112). The associations of SBP_{Slope} and DBP_{Slope} with SHS were not statistically significant (online supplemental table S1).

Relationship among exercise capacity, respiratory symptoms and cardiovascular outputs

To determine whether respiratory symptoms affected the association of exercise capacity with cardiovascular outputs, we included mMRC as an additional predictor in the regression modelling of work versus cardiovascular outputs. In those analyses, SBP_{Slope}, DBP_{Slope} and HR_{Slope} retained their associations and statistical significance, as did having an mMRC of ≥1 (online supplemental table S3).

Moreover, to determine the relationship between O₂-Pulse and blood pressure, we examined the contribution of SBP and DBP to O₂-Pulse, and found that O₂-Pulse at peak exercise was negatively associated with SBP_{Slope} and DBP_{Slope} after adjustment for covariates (online supplemental table S4).

Cardiovascular response measures and baseline air trapping

Given the physical location of lung, heart and great vessels within the thoracic cavity, we examined the potential interaction of baseline air trapping and cardiovascular outputs of exercise. To do this, we examined whether the cardiovascular predictors of exercise capacity including O₂-Pulse (proxy of stroke volume) and blood pressure (SBP and DBP) mediate the association of air trapping (FRC/TLC and RV/TLC) with exercise capacity.

These mediation analyses showed that a substantial fraction of RV/TLC association with exercise capacity (cumulative work (Watt-Minute)) was mediated through RV/TLC effect on O₂-Pulse at peak exercise (39%; p=0.036) (table 6). Although not significant, RV/TLC association with workload (Watt_{Peak}) also seemed to be mediated through O₂-Pulse (36%; p=0.078). Consistent with this finding, the heart rate at peak exercise (HR_{Peak}) also mediated the association of RV/TLC with exercise capacity (mediated 21% and 28% of the total effect of RV/TLC on Watts_{Peak} and Work_{TotalPeak}, respectively; all p<0.05). The mediation analyses of FRC/TLC were not statistically significant (online supplemental table S2).

DISCUSSION

In this observational study of a never-smoking cohort with a history of remote but prolonged exposure to SHS, we found the cohort to have an abnormal cardiovascular response to exercise that was proportional to their SHS exposure. Exercise capacity, as measured by highest workload completed (Watts_{Peak}) or volume of oxygen uptake at peak exercise (VO_{2Peak}), was associated with years of exposure to SHS. Remarkably, over 40% of the association of exercise capacity (Watts_{Peak}) with SHS was dependent on O₂-Pulse_{Peak}, which suggests that the effect of SHS exposure on exercise capacity is importantly

Table 2 Cardiopulmonary testing measurements

Cardiopulmonary exercise testing outputs	All (N=245)	Unexposed (N=106)	Exposed (N=139)	P value
Cardiopulmonary testing measurements				
VO _{2Peak} (L/min)	1.557±0.476	1.800±0.532	1.372±0.324	<0.001
VO _{2Peak} (% predicted)	100±24	102±28	98±21	0.388
Reached 100% predicted VO _{2Peak} (n (%))	114 (46.5)	52 (49.1)	62 (44.6)	0.787
VO _{2Peak} <100% predicted	131 (53.5)	54 (50.9)	77 (55.4)	0.787
VO _{2Peak} <84% predicted	71 (29.0)	30 (28.3)	41 (29.5)	0.979
VO _{2Peak/kg} (mL/min.kg)	23.82±7.02	27.15±7.32	21.28±5.59	<0.001
VO _{2Peak/kg} (% predicted)	85±18	86±21	84±16	0.657
VO _{2Peak/kg} < LLN (n (%))	33 (13.5)	21 (19.8)	12 (8.6)	0.039
VCO _{2Peak} (L/min)	1.90±0.59	2.20±0.64	1.67±0.43	<0.001
Watts _{Peak} (watts)	156±46	181±46	137±36	<0.001
Watts _{Peak} (% predicted)	135±33	142±35	130±31	0.020
Watts per stage (watts)	27±8	30±7	24±7	<0.001
Cumulative work (watt-minute)	566±229	661±252	491±178	<0.001
Stages completed	6.0±1.3	6.1±1.3	6.0±1.3	0.631
Symptoms at peak exercise (modified Borg Dyspnoea Scale 0–10)				
Shortness of Breath	4.2±1.9	4.2±1.9	4.2±1.9	0.996
Effort	5.1±1.9	5.5±1.9	4.9±1.9	0.063
Fatigue	4.7±1.9	4.9±1.8	4.6±1.9	0.342
Dyspnoea _{Peak} (n (%))	117 (49.6)	43 (41.0)	74 (56.5)	0.06
Pulmonary response				
V _{EPeak} (L/min)	57.04±16.97	63.86±18.43	51.84±13.71	<0.001
V _{EPeak} (% predicted)	50±12	50±12	50±12	0.940
RER	1.21±0.13	1.22±0.12	1.21±0.13	0.702
RR _{Peak} (breaths/min)	34.7±9.0	36.1±9.4	33.6±8.5	0.115
RR _{Peak} ≥60 (n/235 (%))	1 (0.4)	1 (1.0)	0 (0)	0.520
V _{TPeak} (L)	1.73±0.47	1.88±0.52	1.62±0.38	<0.001
V _{TPeak} (% predicted)	86±17	87±17	86±17	0.881
V _E /VO _{2Peak}	37.1±6.2	36.0±6.0	37.9±6.2	0.066
V _E /VCO _{2Peak}	30.7±3.8	29.7±3.9	31.5±3.5	<0.001
V _E /VCO _{2Peak} ≥34 (n (%))	51 (20.8)	15 (14.2)	36 (25.9)	0.080
V _E /VCO _{2Peak} (% predicted)	108±12	107±14	109±11	0.729
V _E /VCO _{2Lowest}	29.4±3.4	28.2±3.2	30.3±3.3	<0.001
V _E /VCO _{2Lowest} (% predicted)	103±11	102±10	104±11	0.220
VO ₂ at anaerobic threshold (VO _{2AT}) (L/min)	0.99±0.33	1.17±0.35	0.87±0.25	<0.001
VO ₂ at anaerobic threshold (VO _{2AT}) (%VO _{2Peak})	63±13	63±13	63±13	0.984
VO _{2AT} ≤40% VO _{2Peak} (n/202 (%))	11 (5.5)	3 (3.7)	8 (6.7)	0.652
V _E /VCO ₂ at anaerobic threshold	31.4±3.9	29.6±3.2	32.7±3.8	<0.001
V _E /VCO ₂ at anaerobic threshold (% predicted)	103±11	101±10	105±12	0.082
Cardiovascular response				
HR _{Baseline} (beat/min)	67.5±12.4	66.5±12.3	68.3±12.6	0.531
HR _{Peak} (beat/min)	141.8±17.9	146.9±14.2	138.0±19.5	<0.001
HR _{Peak} (% predicted)	85±10	85±8	86±12	0.911
HR _{Peak} ≤90% predicted (n (%))	165 (67.3)	84 (79.2)	81 (58.3)	0.002

Continued

Table 2 Continued

Cardiopulmonary exercise testing outputs	All (N=245)	Unexposed (N=106)	Exposed (N=139)	P value
HRR	24±17	26±15	23±19	0.394
HRR ≥15 (n (%))	176 (71.8)	89 (84.0)	87 (62.6)	0.001
HR _{Slope} (beat/min/10 Watts)	4.73±1.19	4.42±1.03	4.99±1.25	<0.001
SBP _{Baseline} (mm Hg)	121.1±15.5	118.1±14.1	123.6±16.2	0.023
SBP _{Peak} (mm Hg)	178.8±20.3	178.9±22.3	178.7±18.5	0.999
SBP _{Slope} (mm Hg/10 Watts)	3.90±1.42	3.61±1.21	4.13±1.53	0.017
DBP _{Baseline} (mm Hg)	76.5±8.9	76.0±9.0	76.8±8.9	0.815
DBP _{Peak} (mm Hg)	93.1±9.8	93.7±8.9	92.5±10.6	0.657
DBP _{Slope} (mm Hg/10 Watts)	1.17±0.72	1.07±0.62	1.24±0.79	0.187
HRE (met at least one criterion) (n/226 (%))	149 (65.9)	73 (71.6)	76 (61.3)	0.268
Rise in SBP ≥50 mm Hg (≥60 mm Hg for men)	138 (61.1)	69 (67.6)	69 (55.6)	0.184
SBP _{Peak} ≥190 mm Hg (≥210 mm Hg for men)	45 (19.9)	20 (19.6)	25 (20.2)	0.995
DBP _{Peak} ≥105 mm Hg	24 (10.6)	12 (11.8)	12 (9.7)	0.879
O ₂ -Pulse _{Peak} (mL/beat)	11.0±3.0	12.3±3.5	10.0±2.2	<0.001
O ₂ -Pulse _{Peak} (% predicted)	116±25	120±27	114±23	0.191
Reached 100% predicted O ₂ -Pulse _{Peak} (n (%))	181 (73.9)	84 (79.2)	97 (69.8)	0.248
O ₂ -Pulse _{Peak} <100% predicted (n (%))	64 (26.1)	22 (20.8)	42 (30.2)	0.248
O ₂ -Pulse _{Peak} ≤80% predicted (n (%))	8 (3.3)	3 (2.8)	5 (3.6)	0.946
O ₂ -Pulse _{Baseline} (mL/beat)	3.8±1.0	4.1±1.1	3.6±0.9	<0.001
O ₂ -Pulse _{Slope} (mL/beat/Watt)	0.47±0.11	0.46±0.09	0.49±0.12	0.070
O ₂ -Pulse at anaerobic threshold (mL/beat)	9.1±3.6	10.5±4.0	8.4±3.2	0.003
O ₂ -Pulse at anaerobic threshold (% O ₂ -Pulse _{Peak})	84±30	86±37	83±25	0.912
SpO _{2Baseline}	99±1	99±1	99±1	0.983
SpO _{2Peak}	98±1	99±1	98±1	0.699
Change in SpO ₂ at peak exercise	-0.59±1.4	-0.5±1.6	-0.6±1.3	0.815

Cardiopulmonary measurements in participants who underwent exercise testing. Data are presented as mean±SD. Data are presented as mean±SD. Reference equations: per cent predicted of normal values of cardiopulmonary outputs were calculated using Wassermann *et al* predicted formulas.²⁰

HR_{Peak}, peak heart rate; HRR, heart rate reserve; O₂-Pulse_{Peak}, oxygen uptake per heartbeat at peak exercise; RER, respiratory exchange ratio (VCO₂/VO₂) at peak exercise; RR_{Peak}, peak respiratory rate; VCO_{2Peak}, peak carbon dioxide production; VE_{Peak}, peak minute ventilation value; VO_{2Max.kg}, peak oxygen uptake per kilogram of body weight; VO_{2Peak}, peak oxygen uptake; VT_{Peak}, peak tidal volume; Watts_{Peak}, peak work stage completed in watts.

mediated through SHS effect on stroke volume and cardiac output. Our finding that past exposure to SHS is a predictor of exercise capacity in an O₂-pulse-dependent (a proxy of stroke volume and cardiac output) manner is novel and suggests that SHS exposure has a lasting effect on cardiac function that is observable years after the exposure has ceased. We also found suggestive evidence, which scarcely fell short of statistical significance ($p=0.078$), that pulmonary air trapping (especially elevated RV/TLC) contributes to lower exercise capacity through its effect on O₂-Pulse_{Peak}. The latter finding tends to implicate an interacting lung and heart pathophysiology wherein pulmonary hyperinflation limits cardiac output to further impairs exercise capacity (figure 2). Furthermore, we found over 60% of the participants to have a hypertensive response to exercise, suggesting

that abnormal escalation of blood pressure contributed to lower exercise capacity in this SHS-exposed cohort in whom only a small minority (4.3%) had known history of hypertension, which was well-controlled in all cases.

In previous studies of this cohort of never-smokers with a history of prolonged remote exposure to SHS, we showed the cohort to have an abnormal lung function at rest and abnormal pulmonary response to exercise including (1) reduced diffusing capacity at rest,¹² (2) reduced pulmonary capillary recruitment (as measured by impaired rise in diffusing capacity) during exercise,¹³ (3) decreased small airways airflow indices on spirometry (maximal flow in mid-expiratory and end-expiratory airflows (FEF_{25-75%} and FEF_{75%})),¹² (4) plethysmographic and radiographic evidence of pulmonary air trapping at rest¹⁴ and (5) progressive (dynamic) pulmonary hyperinflation during

Table 3 Associations of exercise capacity with each of the cardiopulmonary exercise outputs or SHS exposure

Independent variables	Dependent variables								
	Peak workload (watt) (Watts _{Peak})			Cumulative work (watt-minute) (Work _{Total})			Peak volume of O ₂ consumption (mL/min) (VO _{2Peak})		
	N	PE ±SEM 95% CI	P value	N	OR ±SEM 95% CI	P value	N	OR ±SEM 95% CI	P value
Cardiovascular outputs									
Peaks									
O ₂ -Pulse _{Peak}	245	10.3±0.7 (8.8 to 11.7)	<0.001	239	53.9±4.6 (44.9 to 62.9)	<0.001		N/A *	
HR _{Peak}	245	0.7±0.1 (0.4 to 0.9)	<0.001	239	4.4±0.7 (3.1 to 5.6)	<0.001	245	8.0±1.1 (5.7 to 10.2)	<0.001
SBP _{Peak}	226	0.3±0.1 (0.1 to 0.5)	0.004	224	2.2±0.6 (1.0 to 3.5)	<0.001	226	3.1±1.1 (0.9 to 5.4)	0.006
DBP _{Peak}	226	0.1±0.2 (-0.3 to 0.5)	0.621	224	0.1±1.2 (-2.4 to 2.5)	0.945	226	0.2±2.2 (-4.2 to 4.6)	0.923
Slopes									
O ₂ -Pulse _{Slope}	238	-64.5±18.1 (-100.1 to -28.9)	<0.001	238	-251.9±109.5 (-467.6 to -36.2)	0.022		N/A *	
HR _{Slope}	238	-11.7±1.9 (-15.5 to -8.0)	<0.001	238	-40.9±11.7 (-63.9 to -17.8)	<0.001	238	-64.1±20.9 (-105.2 to -23.0)	0.002
SBP _{Slope}	227	-7.0±1.5 (-10.1 to -4.0)	<0.001	225	-22.3±9.3 (-40.7 to -4.0)	0.017	227	-44.1±16.6 (-76.8 to -11.4)	0.008
DBP _{Slope}	227	-12.7±3.0 (-18.6 to -6.9)	<0.001	225	-50.0±17.7 (-84.9 to -15.1)	0.005	227	-113.7±31.3 (-175.5 to -52.0)	<0.001
Pulmonary outputs									
RR _{Peak}	235	1.1±0.2 (0.6 to 1.5)	<0.001	233	7.9±1.3 (5.4 to 10.4)	<0.001	235	17.9±2.1 (13.8 to 22.1)	<0.001
VE _{Peak}	245	1.4±0.1 (1.2 to 1.7)	<0.001	239	8.4±0.6 (7.2 to 9.6)	<0.001	245	17.5±0.9 (15.7 to 19.3)	<0.001
VT _{Peak}	239	37.2±5.6 (26.1 to 48.3)	<0.001	237	177.6±33.5 (111.5 to 243.6)	<0.001	239	307.8±59.2 (191.1 to 424.5)	<0.001
VO _{2AT}	202	57.8±7.7 (42.6 to 73.0)	<0.001	200	287.1±47.4 (193.6 to 380.5)	<0.001	202	799.3±71.3 (658.8 to 939.9)	<0.001
VE/VCO _{2Peak}	245	-1.2±0.6 (-2.3 to -0.02)	0.046	239	-0.4±3.4 (-7.2 to 6.4)	0.906	245	-7.9±6.1 (-19.9 to 4.0)	0.191
RV/TLC	235	-1.6±0.5 (-2.5 to -0.6)	0.001	230	-8.6±2.8 (-14.1 to -3.1)	0.002	235	-14.3±5.0 (-24.2 to -4.4)	0.004
FRC/TLC	220	-0.3±0.4 (-1.1 to 0.4)	0.363	219	-2.1±2.2 (-6.5 to 2.2)	0.337	220	-5.0±4.0 (-12.8 to 2.8)	0.210
SHS exposure									
Airline SHS exposure (years)	241	-0.8±0.2 (-1.2 to -0.3)	<0.001	235	-2.3±1.4 (-5.1 to 0.4)	0.092	241	-5.0±2.4 (-9.7 to -0.2)	0.040
Childhood home SHS exposure (Y/N)	245	-0.5±4.1 (-8.7 to 7.6)	0.895	239	4.7±24.3 (-43.1 to 52.5)	0.845	245	-17.7±42.5 (-101.4 to 65.9)	0.676
Adult home SHS exposure (Y/N)	245	-5.1±4.9 (-14.7 to 4.5)	0.292	239	-19.0±28.8 (-75.7 to 37.6)	0.509	245	-50.9±50.2 (-149.7 to 47.9)	0.311

The association between exercise capacity (dependent variable) and each of the cardiopulmonary exercise measures, pulmonary outputs or SHS exposure (independent variable) were individually assessed by multivariable linear regression modeling with adjustment for age, sex, height, body mass index and corresponding baseline values (for slope variables). Statistically significant values are shown in bold.

*The associations of VO_{2Peak} with O₂-Pulse_{Peak} and O₂-Pulse_{Slope} were not computed due to existence of “mathematical coupling” between VO₂ and O₂-Pulse, which depends on VO₂ for its calculation (O₂-Pulse=VO₂/HR).

DBP, diastolic blood pressure; FRC, functional residual capacity; HR, heart rate; O₂-Pulse_{Peak}, oxygen uptake per heartbeat at peak exercise; RR_{Peak}, peak respiratory rate; RV, residual volume; SBP, systolic blood pressure; SHS, secondhand smoke; TLC, total lung capacity; VCO_{2Peak}, peak carbon dioxide production; VE_{Peak}, peak minute ventilation value; VO_{2AT}, oxygen uptake at anaerobic threshold; VO_{2Peak}, peak oxygen uptake; VT_{Peak}, peak tidal volume.

exercise.¹⁴ Overall, these abnormalities are suggestive of presence of an unrecognised early or mild obstructive lung disease that, while not meeting the spirometric definition of COPD, is consistent with an early/mild

disease that could be categorised as ‘pre-COPD’ and could contribute to lower pulmonary reserve and potential adverse health outcomes.^{28 29} In the current study, we found evidence that prolonged exposure to SHS, even



Table 4 Associations of respiratory symptoms with each of the cardiopulmonary exercise outputs and SHS exposure

		Dependent variables							
		Modified Borg Dyspnoea Scale			mMRC Dyspnoea Scale				
		Dyspnoea score \geq either leg fatigue or tiredness score			Having any respiratory symptoms				
Independent variables	N	OR \pm SEM (95% CI)	P value	N	OR \pm SEM (95% CI)	P value	N	OR \pm SEM (95% CI)	P value
Exercise capacity									
VO_{2Peak}	236	1.284 \pm 0.543 (0.562 to 2.977)	0.554	245	0.078\pm0.072 (0.011 to 0.438)	0.005	245	0.475 \pm 0.204 (0.200 to 1.084)	0.082
Watt _{Peak}	236	1.003 \pm 0.004 (0.995 to 1.012)	0.472	245	0.975\pm0.008 (0.958 to 0.991)	0.003	245	0.998 \pm 0.004 (0.989 to 1.006)	0.618
Work _{Total}	235	1.001 \pm 0.001 (0.999 to 1.002)	0.376	239	0.996\pm0.002 (0.993 to 0.999)	0.014	239	0.999 \pm 0.001 (0.998 to 1.001)	0.289
Cardiovascular outputs									
Peaks									
O_2 -Pulse _{Peak}	236	0.992 \pm 0.066 (0.871 to 1.130)	0.905	245	0.808 \pm 0.108 (0.614 to 1.039)	0.110	245	0.929 \pm 0.061 (0.816 to 1.056)	0.264
HR _{Peak}	236	1.008 \pm 0.008 (0.992 to 1.024)	0.337	245	0.969\pm0.013 (0.943 to 0.995)	0.021	245	0.990 \pm 0.008 (0.975 to 1.006)	0.233
SBP _{Peak}	223	1.009 \pm 0.007 (0.994 to 1.023)	0.251	226	1.015 \pm 0.013 (0.990 to 1.043)	0.244	226	0.999 \pm 0.007 (0.984 to 1.013)	0.851
DBP _{Peak}	223	1.030\pm0.015 (1.002 to 1.060)	0.039	226	0.969 \pm 0.023 (0.925 to 1.015)	0.181	226	0.987 \pm 0.014 (0.959 to 1.014)	0.342
Slopes									
O_2 -Pulse _{Slope}	235	0.266 \pm 0.348 (0.02 to 3.423)	0.311	238	2.777 \pm 5.966 (0.040 to 198.051)	0.634	238	0.140 \pm 0.185 (0.010 to 1.835)	0.136
HR _{Slope}	235	1.159 \pm 0.16 (0.886 to 1.526)	0.284	238	1.165 \pm 0.279 (0.725 to 1.865)	0.523	238	1.111 \pm 0.155 (0.845 to 1.463)	0.451
SBP _{Slope}	224	1.068 \pm 0.114 (0.867 to 1.32)	0.535	227	1.714\pm0.354 (1.149 to 2.599)	0.009	227	1.103 \pm 0.118 (0.894 to 1.364)	0.360
DBP _{Slope}	224	1.433 \pm 0.294 (0.962 to 2.161)	0.079	227	1.539 \pm 0.547 (0.761 to 3.092)	0.225	227	1.245 \pm 0.253 (0.836 to 1.865)	0.281
Pulmonary outputs									
RR _{Peak}	230	0.995 \pm 0.016 (0.965 to 1.026)	0.751	235	0.931\pm0.030 (0.872 to 0.988)	0.023	235	0.966\pm0.016 (0.934 to 0.996)	0.031
VE _{Peak}	236	1.002 \pm 0.010 (0.983 to 1.021)	0.854	245	0.931\pm0.020 (0.891 to 0.968)	<0.001	245	0.982 \pm 0.009 (0.964 to 1.001)	0.060

Continued

Table 4 Continued

Dependent variables		mMRC Dyspnoea Scale			FAMRI SHS Questionnaire			
Modified Borg Dyspnoea Scale		Having mMRC ≥1			Having any respiratory symptoms			
Independent variables	OR ±SEM (95% CI)	P value	N	OR ±SEM (95% CI)	P value	N	P value	
VT _{Peak}	1.437±0.584 (0.651 to 3.225)	0.371	239	0.887±0.585 (0.232 to 3.135)	0.855	239	1.018±0.403 (0.466 to 2.219)	0.964
VO _{2AT}	1.067±0.634 (0.331 to 3.439)	0.912	202	0.027±0.033 (0.002 to 0.268)	0.003	202	0.542±0.312 (0.172 to 1.667)	0.287
VE/VCO _{2Peak}	0.953±0.038 (0.879 to 1.028)	0.221	245	0.976±0.073 (0.836 to 1.118)	0.740	245	0.939±0.038 (0.864 to 1.015)	0.126
RV/TLC	0.977±0.032 (0.915 to 1.042)	0.478	235	1.102±0.061 (0.989 to 1.232)	0.079	235	1.061±0.035 (0.996 to 1.134)	0.069
FRC/TLC	1.024±0.026 (0.974 to 1.078)	0.364	220	1.136±0.052 (1.043 to 1.247)	0.004	220	1.032±0.026 (0.983 to 1.085)	0.212
SHS exposure								
Airline SHS exposure (years)	1.009±0.016 (0.978 to 1.042)	0.560	241	0.982±0.026 (0.932 to 1.034)	0.496	241	1.009±0.015 (0.979 to 1.040)	0.556
Childhood home SHS exposure (Y/N)	1.078±0.296 (0.628 to 1.85)	0.784	245	1.660±0.777 (0.671 to 4.289)	0.279	245	2.048±0.563 (1.201 to 3.530)	0.009
Adult home SHS exposure (Y/N)	1.156±0.379 (0.609 to 2.209)	0.657	245	1.113±0.554 (0.401 to 2.882)	0.828	245	2.048±0.660 (1.094 to 3.884)	0.026

Associations of respiratory symptoms at rest (mMRC Dyspnoea Scale and FAMRI SHS Questionnaire) and during exercise (modified Borg Dyspnoea Scale) (dependent variables) with each of the cardiopulmonary exercise measures and SHS exposure (predictors) were assessed by univariate linear regression models with adjustment for age, sex, height, body mass index and corresponding baseline values (for slope predictors). Statistically significant values are shown in bold.

DBP, diastolic blood pressure; FRC, functional residual capacity; HR, heart rate; O₂-Pulse_{Peak}, oxygen uptake per heartbeat at peak exercise; RR_{Peak}, peak respiratory rate; RV, residual volume; SBP, systolic blood pressure; SHS, secondhand smoke; TLC, total lung capacity; VCO_{2Peak}, peak carbon dioxide production; VE_{Peak}, peak minute ventilation value; VO_{2AT}, oxygen uptake at Anaerobic Threshold; VO_{2Peak}, peak oxygen uptake; VT_{Peak}, peak tidal volume.

Table 5 Effect of SHS exposure on exercise capacity through mediators

Mediators	Mediation analysis of effect of SHS exposure to									
	Watts _{Peak}			Work _{Total}			VO _{2Peak}			
	N	% mediated	P value	N	% mediated	P value	N	% mediated	P value	
Cardiovascular outputs										
Peaks										
O ₂ -Pulse _{Peak}	241	40.8 (4.4 to 76.2)	0.038	235	73.6 (-170.7 to 319.8)	0.112		N/A *		
HR _{Peak}	241	0.03 (-33.5 to 21.5)	0.998	235	8.0 (-106.2 to 112.8)	0.750	241	1.6 (-109.5 to 55.6)	0.962	
SBP _{Peak}	223	2.5 (-17.4 to 23.0)	0.718	221	4.8 (-74.5 to 79.9)	0.736	223	3.2 (-53.4 to 42.3)	0.726	
DBP _{Peak}	223	0.2 (-11.9 to 12.9)	0.892	221	0.5 (-28.8 to 47.5)	0.884	223	0.3 (-20.5 to 32.0)	0.894	
Slopes										
O ₂ -Pulse _{Slope}	234	11.7 (-7.4 to 37.9)	0.214	234	14.1 (-81.6 to 101.9)	0.278		N/A *		
HR _{Slope}	234	17.6 (-0.6 to 49.7)	0.058	234	18.9 (-80.6 to 138.7)	0.160	234	13.2 (-4.6 to 75.4)	0.114	
SBP _{Slope}	224	1.7 (-30.5 to 24.0)	0.848	222	0.7 (-53.9 to 38.4)	0.868	224	1.0 (-53.8 to 30.8)	0.882	
DBP _{Slope}	224	1.9 (-31.1 to 25.0)	0.840	222	0.7 (-83.2 to 44.9)	0.934	224	2.1 (-75.4 to 39.1)	0.852	
Pulmonary outputs										
RR _{Peak}	231	7.3 (-19.9 to 34.0)	0.474	229	26.3 (-167.8 to 217.8)	0.294	231	18.1 (-82.2 to 90.2)	0.462	
VE _{Peak}	241	30.0 (-13.4 to 61.7)	0.116	235	70.4 (-166.1 to 277.7)	0.116	241	58.9 (-47.9 to 156.9)	0.106	
VT _{Peak}	235	11.5 (-17.4 to 38.8)	0.300	233	14.8 (-61.5 to 124.4)	0.398	235	13.7 (-35.4 to 74.9)	0.316	
RV/TLC	234	7.3 (-7.0 to 42.2)	0.284	229	10.5 (-59.2 to 134.9)	0.310	234	8.1 (-14.3 to 99.9)	0.318	
FRC/TLC	219	4.3 (-4.8 to 31.1)	0.276	218	5.2 (-30.1 to 73.1)	0.366	219	6.6 (-9.7 to 83.5)	0.256	

To see if the association of SHS exposure (independent variable) with exercise capacity (dependent variable) was mediated through the cardiovascular or pulmonary outputs, mediation analyses were performed with adjustment for age, sex, height and body mass index and inclusion of one mediator at a time. Statistically significant values are shown in bold.

*The associations of VO_{2Peak} with O₂-Pulse_{Peak} and O₂-Pulse_{Slope} were not computed due to existence of “mathematical coupling” between VO₂ and O₂-Pulse, which depends on VO₂ for its calculation (O₂-Pulse=VO₂/HR).

DBP, diastolic blood pressure; FRC, functional residual capacity; HR, heart rate; O₂-Pulse_{Peak}, oxygen uptake per heartbeat at peak exercise; RR_{Peak}, peak respiratory rate; RV, residual volume; SBP, systolic blood pressure; SHS, secondhand smoke; TLC, total lung capacity; VE_{Peak}, peak minute ventilation value; VO_{2Peak}, peak oxygen uptake; VT_{Peak}, peak tidal volume.

when remote, is associated with cardiovascular abnormalities suggestive of occult cardiovascular dysfunction with potential additional contribution from pulmonary hyperinflation. These abnormalities reveal subtle but lower cardiopulmonary functional reserve, manifested here as lower exercise capacity, and implicate a reduced efficiency of the body's oxygen delivery machinery, which could be disadvantageous during the times of increased cardiopulmonary output demands as in physiological distress or disease.

Although it remains unclear how exposure to SHS causes an impairment in cardiac function, an interaction between pulmonary and cardiovascular systems, which occupy the same body cavity (thorax), has been proposed to play a role. Air trapping as measured by lung volumes (FRC/TLC and RV/TLC) is the earliest manifestation of COPD,^{28 29} and is associated with reduced exercise capacity due to ventilatory limitation caused by progressive air trapping and pulmonary hyperinflation.¹⁴ Changes in lung volumes due to pulmonary hyperinflation could cause increased intra-thoracic pressures, particularly during exertion, and thus adversely affect the cardiovascular function.^{23 25} To investigate this possible mechanism, we examined whether air trapping did contribute to exercise capacity through an interaction

with cardiac output by performing a mediation analysis among pulmonary air trapping (FRC/TLC and RV/TLC), cardiac stroke volume (O₂-pulse), and exercise capacity (Watts_{Peak}) (figure 2). Although the analysis did not reach statistical significance (p=0.078 for RV/TLC) and thus could not provide any further corroborating evidence for our hypothesis, the analysis did suggest that a substantial proportion (36%) of air trapping effect on exercise capacity may be mediated through stroke volume.

Other factors that may have contributed to lower O₂-pulse in this setting include impaired left ventricular (LV) filling from myocardial stiffness, and decreased LV systolic emptying in the setting of increased vascular resistance.³⁰ SHS could through pro-inflammatory effects predispose to endothelial dysfunction.³¹ At the level of the coronary microvasculature, endothelial dysfunction can promote cardiomyocyte stiffening and myocardial fibrosis,³² whereas peripherally, it can interfere with normal exercise-related relaxation of the muscular arterioles, increasing afterload.³⁰

As relates to vascular dysfunction, it is notable that 62% of our participants experienced a hypertensive response to exercise, a proportion that exceeds the 30%–40% reported in other settings.^{33–35} Such hypertensive

Table 6 Effect of air trapping on exercise capacity through mediators

Mediators	Mediation analysis of effect of RV/TLC to								
	Watts _{Peak}			Work _{Total}			VO _{2Peak}		
	N	% mediated (95% CI)	P value	N	% mediated (95% CI)	P value	N	% mediated (95% CI)	P value
Cardiovascular outputs									
Peaks									
O ₂ -Pulse _{Peak}	235	35.9 (-6.1 to 69.3)	0.078	230	39.3 (3.3 to 82.7)	0.036		N/A *	
HR _{Peak}	235	20.7 (0.7 to 54.7)	0.044	230	27.6 (2.7 to 74.4)	0.034	235	27.7 (-0.7 to 79.8)	0.052
SBP _{Peak}	220	5.3 (-7.0 to 30.3)	0.390	219	6.8 (-9.0 to 41.9)	0.396	220	5.0 (-6.7 to 31.7)	0.388
DBP _{Peak}	220	0.3 (-4.5 to 10.2)	0.804	219	0.02 (-5.5 to 8.2)	0.978	220	0.04 (-4.6 to 8.0)	0.934
Slopes									
O ₂ -Pulse _{Slope}	229	11.5 (-5.7 to 32.4)	0.192	229	10.3 (-5.1 to 34.0)	0.194		N/A *	
HR _{Slope}	229	2.4 (-13.3 to 32.4)	0.794	229	1.4 (-10.6 to 23.0)	0.794	229	1.2 (-9.7 to 19.6)	0.792
SBP _{Slope}	221	6.9 (-4.9 to 24.1)	0.248	220	3.6 (-4.6 to 19.4)	0.340	221	4.9 (-3.4 to 21.7)	0.278
DBP _{Slope}	221	0.3 (-18.6 to 13.9)	0.970	220	0.2 (-17.6 to 13.0)	0.968	221	0.3 (-20.1 to 15.1)	0.968
Pulmonary outputs									
RR _{Peak}	225	1.3 (-17.1 to 30.8)	0.882	224	2.2 (-22.9 to 48.2)	0.858	225	2.3 (-25.5 to 64.7)	0.882
VE _{Peak}	235	75.1 (42.7 to 137.8)	0.002	230	85.9 (49.4 to 173.5)	0.002	235	98.0 (64.2 to 204.2)	<0.001
VT _{Peak}	229	44.9 (21.2 to 93.6)	<0.001	228	43.1 (17.6 to 107.8)	0.004	229	37.5 (15.0 to 91.4)	0.002

To see if the association of air trapping (independent variable) with exercise capacity (dependent variable) was mediated through the cardiovascular or pulmonary outputs, mediation analyses were performed with adjustment for age, sex, height and body mass index and inclusion of one mediator at a time. Statistically significant values are shown in bold.

*The associations of VO_{2Peak} with O₂-Pulse_{Peak} and O₂-Pulse_{Slope} were not computed due to existence of “mathematical coupling” between VO₂ and O₂-Pulse, which depends on VO₂ for its calculation (O₂-Pulse=VO₂/HR).

DBP, diastolic blood pressure; HR, heart rate; O₂-Pulse_{Peak}, oxygen uptake per heartbeat at peak exercise; RR_{Peak}, peak respiratory rate; RV, residual volume; SBP, systolic blood pressure; SHS, secondhand smoke; TLC, total lung capacity; VE_{Peak}, peak minute ventilation value; VO_{2Peak}, peak oxygen uptake; VT_{Peak}, peak tidal volume.

response has been linked to both LV systolic and diastolic dysfunction,^{36 37} as well as to increased risk of cardiovascular events.^{38–40} Although we did not detect a relationship between hypertensive response to exercise and SHS,

this does not exclude a role for abnormal arterial impedance with exercise as a potential mechanism underlying the SHS-associated diminution in stroke volume.³⁰ Indeed, further research will be necessary to delineate the relative contributions of cardiopulmonary interaction, myocardial disease and vascular dysfunction to exercise intolerance in the context of exposure to direct or indirect smoke.

Our study has limitations that should be kept in view. First, there may be concerns about the generalisability of the findings because the cohort studied are mostly women, which reflects the demographics of those who worked in airlines as flight crew in the latter half of the last century when smoking in aircraft cabin was permitted. The choice to study flight crews permitted overcoming the challenge of long-term SHS exposure assessment by allowing estimation of a more objective and reproducible exposure index based on employment history and the smoking ban timeline on domestic and international flights of different airlines.¹² Women have been reported to be more susceptible to adverse health effects of tobacco smoke,⁴¹ such that the findings are not necessarily generalisable to men. Second, the cardiovascular findings reported in this study are mainly derived from CPET with no imaging (such as echocardiography and MRI) or invasive haemodynamic monitoring to provide additional robust evidence to corroborate our findings. Such studies are needed and are in progress (

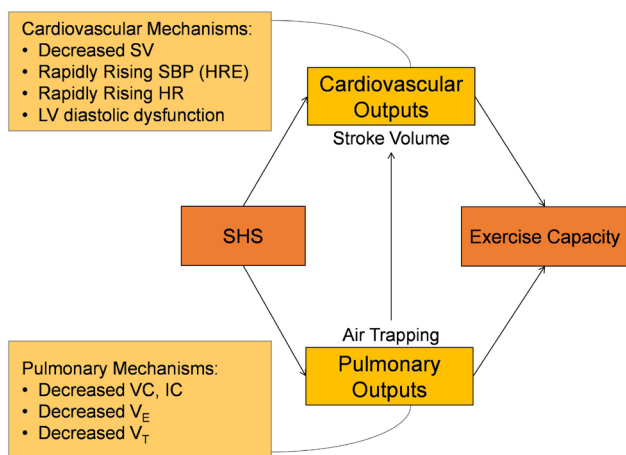


Figure 2 Proposed model for interaction of SHS with cardiovascular and pulmonary contributors to exercise capacity. Illustration of mediation effects between SHS exposure and exercise capacity. HR, heart rate; HRE, hypertensive response to exercise; IC, inspiratory capacity; SHS, secondhand tobacco smoke; SV, cardiac stroke volume; VC, vital capacity; VE, minute ventilation; VT, volume of tidal breathing.



ClinicalTrials.gov Identifier: NCT04715568). Nevertheless, studies describing cardiovascular health effects of *direct* smoking using echocardiography and MRI have been previously reported, which corroborate our findings.^{42–43} Our report, however, is the first to describe the chronic and long-term cardiovascular health effects due to past prolonged exposure to SHS. Third, while we found association of exercise capacity ($Watts_{Peak}$) with years of SHS exposure, the association of respiratory symptoms with SHS was less striking and less consistent across the different questionnaire platforms. However, it is not uncommon to see differences in scores across different respiratory questionnaires,⁴⁴ and similarly, baseline respiratory symptoms (mMRC Dyspnoea Scale and UCSF FAMRI SHS questionnaire) may measure different things and thus produce different scores compared with those done at peak exercise (modified Borg Dyspnoea Scale). For example, participants who had impairments at baseline and thus were more symptomatic are likely to not perform as well during the exercise and thus may report lesser symptoms in a sub-maximal effort exercise test.

In conclusion, healthy never-smokers with history of remote but prolonged exposure to SHS have an abnormal cardiovascular response to exercise, which is characterised by a stroke volume (oxygen-pulse) and thus an exercise capacity that are reduced proportional to their years of exposure to SHS. The mechanisms by which past exposure to SHS may limit stroke volume and thus exercise capacity are not entirely clear. But impaired LV filling and emptying may be involved, with contributions from pulmonary hyperinflation (beyond ventilatory limitation) and vascular dysfunction, both peripherally and centrally. Overall, the abnormal cardiovascular response to exercise in this population reveals the presence of subclinical pathology that impairs the cardiopulmonary functional reserve and reduces the efficiency of body's oxygen delivery machinery, which could be disadvantageous during the times of increased cardiopulmonary output demands as in physiological distress or disease.

Author affiliations

¹Department of Biomedical Informatics and Medical Education, University of Washington, Seattle, Washington, USA

²Pulmonary and Critical Care Section, San Francisco Veterans Affairs Health Care System, San Francisco, California, USA

³Department of Medicine, University of California, San Francisco, California, USA

⁴Cardiology Section, San Francisco Veterans Affairs Medical Center, San Francisco, California, USA

⁵Department of Epidemiology and Biostatistics, University of California, San Francisco, California, USA

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Contributors Conceived and designed the current manuscript study: MA. Developed study protocols: WMG, MA. Collected samples and data: SZ, MD, WMG, MA. Analysed and interpreted data: SZ, MD, JRK, MA. Prepared and edited the manuscript: SZ, MD, WMG, JRK, MA. Obtained funding: SZ, MA. Guarantor: MA. All authors read and agreed to the published version of the manuscript.

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ORCID iDs

Siyang Zeng <http://orcid.org/0000-0001-9346-301X>

Mehrdad Arjomandi <http://orcid.org/0000-0002-0116-9217>

REFERENCES

- Centers for Disease Control and Prevention. Vital Signs: Disparities in Nonsmokers' Exposure to Secondhand Smoke - United States, 1999–2012, 2015. Available: https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6404a7.htm?s_cid=mm6404a7_w [Accessed 28 Nov 2018].
- GBD 2015 Tobacco Collaborators. Smoking prevalence and attributable disease burden in 195 countries and territories, 1990–2015: a systematic analysis from the global burden of disease study 2015. *Lancet* 2017;389:1885–906.
- Tsai J, Homa DM, Gentzke AS, et al. Exposure to Secondhand Smoke Among Nonsmokers - United States, 1988–2014. *MMWR Morb Mortal Wkly Rep* 2018;67:1342–6.
- Barnoya J, Glantz SA. Cardiovascular effects of secondhand smoke: nearly as large as smoking. *Circulation* 2005;111:2684–98.
- Meyers DG, Neuberger JS, He J. Cardiovascular effect of bans on smoking in public places: a systematic review and meta-analysis. *J Am Coll Cardiol* 2009;54:1249–55.
- Yankelevitz DF, Henschke CI, Yip R, et al. Second-Hand tobacco smoke in never smokers is a significant risk factor for coronary artery calcification. *JACC Cardiovasc Imaging* 2013;6:651–7.
- The health consequences of involuntary exposure to tobacco smoke: a report of the surgeon General. Atlanta (GA) 2006.
- The health consequences of Smoking-50 years of progress: a report of the surgeon General. Atlanta (GA) 2014.
- Secondhand Smoke Exposure and Cardiovascular Effects: Making Sense of the Evidence. Washington (DC) 2010.
- Repache J. Flying the smoky skies: secondhand smoke exposure of flight attendants. *Tob Control* 2004;13 Suppl 1:8i–19.
- Benowitz NL, Bernert JT, Caraballo RS, et al. Optimal serum cotinine levels for distinguishing cigarette smokers and nonsmokers within different racial/ethnic groups in the United States between 1999 and 2004. *Am J Epidemiol* 2009;169:236–48.

- 12 Arjomandi M, Haight T, Redberg R, *et al.* Pulmonary function abnormalities in never-smoking flight attendants exposed to secondhand tobacco smoke in the aircraft cabin. *J Occup Environ Med* 2009;51:639–46.
- 13 Arjomandi M, Haight T, Sadeghi N, *et al.* Reduced exercise tolerance and pulmonary capillary recruitment with remote secondhand smoke exposure. *PLoS One* 2012;7:e34393.
- 14 Arjomandi M, Zeng S, Geerts J, *et al.* Lung volumes identify an at-risk group in persons with prolonged secondhand tobacco smoke exposure but without overt airflow obstruction. *BMJ Open Respir Res* 2018;5:e000284.
- 15 Eisner MD, Wang Y, Haight TJ, *et al.* Secondhand smoke exposure, pulmonary function, and cardiovascular mortality. *Ann Epidemiol* 2007;17:364–73.
- 16 Fletcher CM, Elmes PC, Fairbairn AS, *et al.* The significance of respiratory symptoms and the diagnosis of chronic bronchitis in a working population. *Br Med J* 1959;2:257–66.
- 17 Borg G. *Borg's perceived exertion and pain scales*. Champaign, IL, US: Human Kinetics, 1998.
- 18 Quanjer PH, Stanojevic S, Cole TJ, *et al.* Multi-Ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. *Eur Respir J* 2012;40:1324–43.
- 19 Stocks J, Quanjer PH. Reference values for residual volume, functional residual capacity and total lung capacity. ats workshop on lung volume measurements. official statement of the European respiratory Society. *Eur Respir J* 1995;8:492–506.
- 20 Wasserman K, Hansen J, Sue D. *Principles of exercise testing and interpretation*. 4th edn. Philadelphia, USA: Lippincott Williams & Wilkins, 2004.
- 21 American Thoracic Society, American College of Chest Physicians. ATS/ACCP statement on cardiopulmonary exercise testing. *Am J Respir Crit Care Med* 2003;167:211–77.
- 22 Moreno LF, Stratton HH, Newell JC, *et al.* Mathematical coupling of data: correction of a common error for linear calculations. *J Appl Physiol* 1986;60:335–43.
- 23 Watz H. The lungs and the heart. *Am J Respir Crit Care Med* 2015;192:7–8.
- 24 Smith BM, Kawut SM, Bluemke DA, *et al.* Pulmonary hyperinflation and left ventricular mass. *Circulation* 2013;127:1503–11.
- 25 Cuttica MJ, Colangelo LA, Shah SJ, *et al.* Loss of lung health from young adulthood and cardiac phenotypes in middle age. *Am J Respir Crit Care Med* 2015;192:76–85.
- 26 Butler J, Schrijen F, Henriquez A, *et al.* Cause of the raised wedge pressure on exercise in chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1988;138:350–4.
- 27 Tingley D, Yamamoto T, Hirose K. Mediation: R package for causal mediation analysis 2014;59:38.
- 28 Arjomandi M, Zeng S, Barjaktarevic I, *et al.* Radiographic lung volumes predict progression to COPD in smokers with preserved spirometry in SPIROMICS. *Eur Respir J* 2019;54:1802214.
- 29 Zeng S, Tham A, Bos B, *et al.* Lung volume indices predict morbidity in smokers with preserved spirometry. *Thorax* 2019;74:114–24.
- 30 Borlaug BA. Mechanisms of exercise intolerance in heart failure with preserved ejection fraction. *Circ J* 2014;78:20–32.
- 31 Messner B, Bernhard D. Smoking and cardiovascular disease: mechanisms of endothelial dysfunction and early atherogenesis. *Arterioscler Thromb Vasc Biol* 2014;34:509–15.
- 32 Paulus WJ, Tschöpe C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. *J Am Coll Cardiol* 2013;62:263–71.
- 33 Le V-V, Mitiku T, Sungar G, *et al.* The blood pressure response to dynamic exercise testing: a systematic review. *Prog Cardiovasc Dis* 2008;51:135–60.
- 34 Scott JA, Coombes JS, Prins JB, *et al.* Patients with type 2 diabetes have exaggerated brachial and central exercise blood pressure: relation to left ventricular relative wall thickness. *Am J Hypertens* 2008;21:715–21.
- 35 Kramer CK, Leitão CB, Canani LH, *et al.* Blood pressure responses to exercise in type II diabetes mellitus patients with masked hypertension. *J Hum Hypertens* 2009;23:620–2.
- 36 Mottram PM, Haluska B, Yuda S, *et al.* Patients with a hypertensive response to exercise have impaired systolic function without diastolic dysfunction or left ventricular hypertrophy. *J Am Coll Cardiol* 2004;43:848–53.
- 37 Takamura T, Onishi K, Sugimoto T, *et al.* Patients with a hypertensive response to exercise have impaired left ventricular diastolic function. *Hypertens Res* 2008;31:257–63.
- 38 Filipovský J, Ducimetière P, Safar ME. Prognostic significance of exercise blood pressure and heart rate in middle-aged men. *Hypertension* 1992;20:333–9.
- 39 Manolio TA, Burke GL, Savage PJ, *et al.* Exercise blood pressure response and 5-year risk of elevated blood pressure in a cohort of young adults: the cardia study. *Am J Hypertens* 1994;7:234–41.
- 40 Tsumura K, Hayashi T, Hamada C, *et al.* Blood pressure response after two-step exercise as a powerful predictor of hypertension: the Osaka health survey. *J Hypertens* 2002;20:1507–12.
- 41 Allen AM, Oncken C, Hatsukami D. Women and smoking: the effect of gender on the epidemiology, health effects, and cessation of smoking. *Curr Addict Rep* 2014;1:53–60.
- 42 Kamimura D, Cain LR, Mentz RJ, *et al.* Cigarette smoking and incident heart failure. *Circulation* 2018;137:2572–82.
- 43 Nadruz W, Claggett B, Gonçalves A, *et al.* Smoking and cardiac structure and function in the elderly: the ARIC study (atherosclerosis risk in communities). *Circ Cardiovasc Imaging* 2016;9:e004950.
- 44 Rutten-van Mölken M, Roos B, Van Noord JA. An empirical comparison of the St George's respiratory questionnaire (SGRQ) and the chronic respiratory disease questionnaire (CRQ) in a clinical trial setting. *Thorax* 1999;54:995–1003.
- 45 Crapo RO, Morris AH, Gardner RM. Reference values for pulmonary tissue volume, membrane diffusing capacity, and pulmonary capillary blood volume. *Bull Eur Physiopathol Respir* 1982;18:893–9.