Associations between lung and endothelial function in early middle age

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ABSTRACT

Background and objective: Chronic lung disease is associated with impaired endothelial function and this may be a risk factor for poor cardiovascular health. It is unknown if there is an association between lung and endothelial function in the general population. We investigated associations between lung and endothelial function in a population-based cohort of 38-year-old men and women.

Methods: Systemic endothelial function was measured using peripheral arterial tonometry to calculate the Framingham reactive hyperaemia index. Lung function was assessed using spirometry, plethysmographic lung volumes, airway conductance and gas transfer. Associations between lung and endothelial function were assessed with and without adjustment for potential confounding factors using regression analyses.

Results: Sex modified the association between lung and endothelial function. Among women, lower values of pre- and post-bronchodilator spirometry, total lung capacity and functional residual capacity (FRC) were associated with worse endothelial function (P < 0.05). These associations persisted after adjustment for smoking, asthma diagnoses, fitness and body mass index. Associations were weaker among men: only FRC, airway conductance and post-bronchodilator forced expiratory volume in 1 s (FEV1)/forced vital capacity (FVC) ratios were associated with endothelial function. Endothelial function was not associated with gas transfer in either sex.

Conclusion: Lower lung volumes and airflow obstruction are associated with endothelial dysfunction among women. There is weaker evidence for an association between airway and endothelial function in men. These findings may partly explain the increased risk of cardiovascular disease among people with poor lung function, but suggest that there are sex differences in this association.

INTRODUCTION

People with impaired lung function have a higher risk of cardiovascular disease. The mechanism for this association is poorly understood and is only partly explained by the shared risk factor of smoking, because low lung function is associated with cardiac disease among people who have never smoked. Elucidating why poor lung function is linked to higher cardiovascular risk is important, given that cardiovascular disease is a leading cause of morbidity and mortality among patients with respiratory diseases.1

Endothelial dysfunction is one possible mechanism linking cardiovascular and respiratory health. The vascular endothelium plays a central role in vascular tone, blood flow and the response to inflammation. Non-invasive measures of endothelial function predict the risk of future cardiovascular events. Impaired endothelial function has been reported in both COPD and asthma, and the extent of endothelial dysfunction is associated with the severity of airflow obstruction. Assessing the pulmonary endothelium is difficult, but it has been suggested that airway inflammation causes endothelial dysfunction in the pulmonary circulation, which leads to systemic endothelial dysfunction. Conversely, it is possible that cardiovascular disease causes systemic and pulmonary endothelial dysfunction and thereby influences lung function.
Evidence for an association between respiratory and endothelial function is mostly based on studies on patients with COPD and smokers. The extent to which the observed associations are due to airway inflammation or are confounded by common risk factors such as smoking and obesity is unclear. We hypothesized that greater lung function would be associated with better endothelial function independently of smoking, obesity and asthma, and assessed this in a population-based cohort of 38-year-olds.\textsuperscript{14-16}

METHODS

The Dunedin Multidisciplinary Health and Development Study is a longitudinal investigation of health and behaviour in an unselected cohort of individuals born during 1972/1973 (http://dunedinstudy.otago.ac.nz).\textsuperscript{14-17} The cohort was formed when 1037 children living in the Dunedin area (91% of eligible births) were assessed at age 3 years. Study members represent the full range of socio-economic status in the South Island of New Zealand and are primarily of New Zealand/European ethnicity. Ninety-five percent (961/1007) of living study members participated in the assessment at age 38 years. Written informed consent was obtained. The Otago Ethics Committee approved the study.

Asthma was defined as a self-reported diagnosis with compatible symptoms or asthma medication within the previous year.\textsuperscript{16} Current smoking was defined as daily smoking for at least 1 month in the previous year. Cumulative tobacco exposure was quantified in pack-years (equivalent to 20 cigarettes/day for 1 year).\textsuperscript{16} Spirometry (forced expiratory volume in 1 s (FEV\textsubscript{1}), forced vital capacity (FVC) and FEV\textsubscript{1}/FVC), total lung capacity (TLC), functional residual capacity (FRC), residual volume (RV), specific airway conductance adjusted for thoracic gas volume (sGaw), transfer factor for carbon monoxide (TL\textsubscript{CO}) and transfer factor corrected for alveolar volume (TL\textsubscript{CO}/VA) were measured using a Vmax body plethysmograph (Care Fusion, Yorba Linda, CA, USA).\textsuperscript{18} Spirometry was repeated after inhalation of 200 μg salbutamol via a large volume spacer. Exhaled carbon monoxide was measured twice before measurement of TL\textsubscript{CO} (MicroCO, Micromedical, Rochester, UK) and the mean value was recorded. Participants were asked to avoid using any inhalers on the day of the test. Equipment was calibrated daily and regular quality control measures were obtained to ensure accuracy and precision of test equipment.

Endothelial function was assessed in the morning in the non-fasting state after lying supine for 10 min in a temperature-controlled room at 20°C (see Appendix S1, Supplementary Information, for further details).\textsuperscript{15} A peripheral arterial tonometry device was placed on the index finger of each hand (Endo-PAT2000, Itamar Medical, Caesarea, Israel). A blood pressure cuff was placed on the right upper arm before recording 2 min of baseline measurements. The cuff was then inflated to 200 or 60 mm Hg above systolic blood pressure, whichever was higher, and occlusion of flow was confirmed. After 5 min, the cuff was deflated and recording continued for 5 min. Pulse amplitude was recorded from both fingers and analysed by a computerized algorithm that provided the average pulse amplitude for each 30-s interval after cuff deflation. The mean pulse amplitudes between 90 and 120 s after cuff deflation divided by mean baseline amplitudes were calculated for the occluded (reactive hyperaemia in the occluded arm, RHo) and control arm (reactive hyperaemia in the control arm, RHc). The Framingham reactive hyperaemia index was defined as the natural logarithm of RHo/RHc.\textsuperscript{15} Higher values of the Framingham reactive hyperaemia index indicate better endothelial function.

Aerobic fitness was measured using a sub-maximal exercise test as previously described.\textsuperscript{19,20} Participants exercised on a cycle ergometer (Monarch, Sweden) for 6–8 min to achieve a stable heart rate around 70% of the predicted maximum (calculated as 220 minus age). From the workload achieved and the final stable heart rate, maximum oxygen uptake at peak exercise (VO\textsubscript{2max} in L/min) was estimated.\textsuperscript{21}

Blood was drawn at the end of the assessment day. C-reactive protein (CRP) was measured using a high-sensitivity immunoturbidimetric assay (Roche Diagnostics, Manheim, Germany) and values were log-transformed to approximate a normal distribution. Haemoglobin (Hb) was measured on an automated analyser (Sysmex Corporation, Kobe, Japan). Oestradiol was measured using a competitive electrochemiluminescence immunoassay (Roche Diagnostics).

Statistical analysis

Associations between lung function and endothelial function were analysed by linear regression using Framingham reactive hyperaemia index as the dependent variable and lung function values as the main predictors in separate analyses. Initial analyses tested for interactions between spirometry, sex, smoking and asthma. All analyses were adjusted for height. Analyses of TL\textsubscript{CO} and TL\textsubscript{CO}/VA also adjusted for Hb and exhaled carbon monoxide. Analyses were repeated with further adjustment for body mass index (BMI), current asthma, cumulative smoking, logCRP and estimated VO\textsubscript{2max}.

Sensitivity analyses excluded participants with asthma or any inhaler treatment in the past year, and those reporting heart disease, diabetes, any form of cancer or arthritis. Because the initial analyses indicated that associations between lung and endothelial function were modified by sex, additional post hoc analyses assessed whether blood oestradiol levels influenced associations between lung and endothelial function. Pregnant women (n = 9) were excluded, but otherwise analyses used all available data. Regression models were checked by visual inspection of histograms of the residuals, residual versus fitted plots and leverage versus squared-residual plots.

RESULTS

Lung and endothelial function data were available for 904 non-pregnant study members (90% of the living cohort; Fig. 1). Mean values of lung function and

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Framingham reactive hyperaemia index are shown in Table 1. Women had higher Framingham reactive hyperaemia index values than men ($P < 0.001$). Mean Framingham reactive hyperaemia index values were slightly, but not significantly, lower among participants with asthma ($-0.06, 95\%\ CI: -0.12$ to $0.01, P = 0.079$) and current smokers ($-0.05, 95\%\ CI: -0.10$ to $0.01, P = 0.089$) after adjusting for sex. Mean values of lung function and Framingham reactive hyperaemia index among participants without

![Flow diagram of participation in this analysis. A small number of participants either refused or were unable to perform valid spirometry or endothelial function tests.](image)

### Table 1 Mean values of lung function and FRHI

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th>Men</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>n Mean SD</td>
<td>n Mean SD</td>
</tr>
<tr>
<td>FRHI</td>
<td>444 0.71 0.39</td>
<td>460 0.50 0.35</td>
</tr>
<tr>
<td>FEV₁ (L)</td>
<td>444 3.13 0.44</td>
<td>460 4.16 0.61</td>
</tr>
<tr>
<td>FVC (L)</td>
<td>444 4.06 0.54</td>
<td>460 5.56 0.75</td>
</tr>
<tr>
<td>FEV₁/FVC</td>
<td>444 0.77 0.06</td>
<td>460 0.75 0.07</td>
</tr>
<tr>
<td>TLC (L)</td>
<td>443 5.69 0.75</td>
<td>456 7.52 0.97</td>
</tr>
<tr>
<td>FRC (L)</td>
<td>443 2.60 0.61</td>
<td>458 3.16 0.78</td>
</tr>
<tr>
<td>RV (L)</td>
<td>443 1.60 0.37</td>
<td>457 1.90 0.43</td>
</tr>
<tr>
<td>sGaw (mL/s/cm H₂O/L)</td>
<td>442 0.18 0.05</td>
<td>458 0.17 0.06</td>
</tr>
<tr>
<td>TLCO (mmol/min/kPa)</td>
<td>442 22.7 3.3</td>
<td>456 31.6 5.1</td>
</tr>
<tr>
<td>TLCO/VA (mmol/min/kPa/L)</td>
<td>442 4.54 0.65</td>
<td>456 4.70 0.67</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>443 26.8 5.8</td>
<td>460 27.4 4.5</td>
</tr>
<tr>
<td>$V'O₂_{max}$ (L/min)</td>
<td>426 1.67 0.19</td>
<td>453 2.96 0.32</td>
</tr>
<tr>
<td>Asthma</td>
<td>444 79 (18)</td>
<td>460 74 (16)</td>
</tr>
<tr>
<td>Current smokers</td>
<td>444 107 (24)</td>
<td>460 134 (29)</td>
</tr>
<tr>
<td>n Median IQR</td>
<td>232 8.6 3.8–16.4</td>
<td>226 13.3 5.8–19.9</td>
</tr>
</tbody>
</table>

Pregnant women and participants not undertaking endothelial function tests or any measure of lung function are excluded.

Pack-years analysis restricted to participants who have ever smoked.

BMI, body mass index; FEV₁, forced expiratory volume in 1 s; FRC, functional residual capacity; FRHI, Framingham reactive hyperaemia index; FVC, forced vital capacity; IQR, interquartile range; RV, residual volume; sGaw, specific airway conductance adjusted for thoracic gas volume; TLC, total lung capacity; TLCO, transfer factor for carbon monoxide; VA, alveolar volume; $V'O₂_{max}$, maximum oxygen uptake at peak exercise.
asthma are shown in Table S1 (Supplementary Information).

There were statistically significant interactions between sex and FEV₁ (P = 0.003) and FVC (P = 0.044) in the prediction of endothelial function, indicating that sex modified the associations between lung and endothelial function (Table 2). Therefore, all subsequent analyses were conducted separately for women and men. There were no significant interactions between spirometry and either asthma diagnosis, current or pack-years smoking in either sex (P values ≥ 0.064).

In regression analyses adjusted for height, greater values of FEV₁, FVC, FEV₁/FVC, TLC and FRC were associated with higher Framingham reactive hyperaemia index values among women (Table 2, Fig. 2). Associations between lung function and the Framingham reactive hyperaemia index were weaker among men and only significant for FRC and sGaw, although a borderline significant association was noted for FEV₁/FVC. There was no association of RV, TLCO or TLCO/VA with the Framingham reactive hyperaemia index in either sex.

Associations between lung and endothelial function among women were similar after adjusting for BMI, current asthma, cumulative smoking, logCRP and estimated V̇O₂max. In this analysis, the association with sGaw became significant (Table 3). Endothelial function was statistically significantly associated with FEV₁/FVC ratio and sGaw in the adjusted analyses in men, but the association with FRC was not.

Findings were substantially unchanged among women after excluding participants with current asthma or inhaler treatment, although the association with FEV₁/FVC was of borderline statistical significance. No associations were statistically significant in men in this analysis (Table S2, Supplementary Information). Associations among women were also similar after further exclusion of participants reporting asthma, heart disease, cancer, diabetes or arthritis, except that the association with TLC and FVC in women was not statistically significant while the association with sGaw became significant (Table S3, Supplementary Information). Among men, only sGaw was significantly associated with endothelial function in this analysis.

Analyses using post-bronchodilator spirometry as the predictors provided similar findings with the exception that the associations with FEV₁/FVC were statistically significant for men (Table S4, Supplementary Information). Endothelial function was not associated with the FEV₁ response to bronchodilator in either sex (P values > 0.41).

Oestradiol levels were not associated with lung or endothelial function in women and adjusting the analyses for oestradiol made no material difference to the associations between lung and endothelial function (data not shown).

**DISCUSSION**

This cross-sectional analysis of lung and endothelial function in a population-based cohort of 38-year olds found that higher values of lung function were associated with better endothelial function among women. These associations were found for a range of dynamic and static lung volumes but the strongest associations were found for FEV₁ and the FEV₁/FVC ratio suggesting that the impaired endothelial function was primarily associated with an obstructive pattern of lung function impairment. Associations between lung and endothelial function among men were generally weaker, although there was a significant association between better endothelial function and specific airway conductance and a tendency to an association with the FEV₁/FVC ratio, which was statistically significant after adjustment for potential confounding and for post-bronchodilator spirometry. We found no evidence for an association between endothelial function and gas transfer in either sex.

Table 2  Height-adjusted regression analyses of associations between endothelial function and lung function

<table>
<thead>
<tr>
<th>Main predictor</th>
<th>Women</th>
<th></th>
<th></th>
<th></th>
<th>Men</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Coefficient (95% CI)</td>
<td>Beta</td>
<td>P</td>
<td>n</td>
<td>Coefficient (95% CI)</td>
<td>Beta</td>
<td>P</td>
</tr>
<tr>
<td>FEV₁ (L)</td>
<td>444</td>
<td>0.23 (0.13 to 0.32)</td>
<td>0.26</td>
<td>&lt;0.001</td>
<td>460</td>
<td>0.05 (−0.01 to 0.10)</td>
<td>0.08</td>
<td>0.111</td>
</tr>
<tr>
<td>FVC (L)</td>
<td>444</td>
<td>0.12 (0.037 to 0.19)</td>
<td>0.16</td>
<td>0.004</td>
<td>460</td>
<td>0.01 (−0.04 to 0.06)</td>
<td>0.02</td>
<td>0.726</td>
</tr>
<tr>
<td>FEV₁/FVC ratio</td>
<td>444</td>
<td>0.78 (0.23 to 1.34)</td>
<td>0.13</td>
<td>0.006</td>
<td>460</td>
<td>0.42 (−0.04 to 0.88)</td>
<td>0.08</td>
<td>0.072</td>
</tr>
<tr>
<td>TLC (L)</td>
<td>443</td>
<td>0.08 (0.02 to 0.14)</td>
<td>0.16</td>
<td>0.006</td>
<td>456</td>
<td>0.00 (−0.04 to 0.04)</td>
<td>−0.01</td>
<td>0.930</td>
</tr>
<tr>
<td>FRC (L)</td>
<td>443</td>
<td>0.13 (0.07 to 0.19)</td>
<td>0.20</td>
<td>&lt;0.001</td>
<td>458</td>
<td>0.05 (0.00 to 0.09)</td>
<td>0.10</td>
<td>0.041</td>
</tr>
<tr>
<td>RV (L)</td>
<td>443</td>
<td>0.09 (−0.18 to 0.19)</td>
<td>0.08</td>
<td>0.105</td>
<td>457</td>
<td>−0.03 (−0.11 to 0.05)</td>
<td>−0.04</td>
<td>0.416</td>
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<tr>
<td>sGaw (mL/s/cm H₂O/L)</td>
<td>442</td>
<td>0.68 (−0.04 to 1.41)</td>
<td>0.09</td>
<td>0.064</td>
<td>458</td>
<td>0.85 (0.29 to 1.41)</td>
<td>0.14</td>
<td>0.003</td>
</tr>
<tr>
<td>TLCO (mmol/min/kPa/L)</td>
<td>430</td>
<td>0.012 (0.007 to 0.025)</td>
<td>0.10</td>
<td>0.084</td>
<td>441</td>
<td>0.004 (−0.004 to 0.012)</td>
<td>0.06</td>
<td>0.336</td>
</tr>
<tr>
<td>TLCO/VA (mmol/min/kPa/L)</td>
<td>432</td>
<td>−0.013 (−0.075 to 0.050)</td>
<td>−0.02</td>
<td>0.694</td>
<td>441</td>
<td>0.033 (−0.023 to 0.089)</td>
<td>0.06</td>
<td>0.249</td>
</tr>
</tbody>
</table>

Analyses by linear regression using Framingham reactive hyperaemia index as the dependent variable and measures of lung function as the main predictors. Coefficients represent the difference in Framingham reactive hyperaemia index associated with unit differences in measures of lung function. Beta coefficients represent the SD (z-score) differences in Framingham reactive hyperaemia index associated with SD differences in measures of lung function. Analyses using TLCO and TLCO/VA are also adjusted for exhaled carbon monoxide and haemoglobin.

FEV₁, forced expiratory volume in 1 s; FRC, functional residual capacity; FVC, forced vital capacity; RV, residual volume; sGaw, specific airway conductance adjusted for thoracic gas volume; TLC, total lung capacity; TLCO, transfer factor for carbon monoxide; VA, alveolar volume.

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The findings for women support our hypothesis that impaired lung function is associated with endothelial dysfunction. These associations were independent of smoking, obesity, asthma, systemic inflammation and aerobic exercise capacity. The pattern and strength of the associations between lung and endothelial function among women were substantially unchanged after excluding participants reporting asthma or inhaler treatment and those with heart disease, arthritis or cancer (Tables S2, S3, Supplementary Information). The associations between lung and endothelial function among men were less convincing. However, the associations between endothelial function and specific airway conductance and the FEV1/FVC ratio observed in several analyses also support an association between impaired endothelial function and airflow obstruction.

The difference in strength of associations between the sexes was unexpected. It is not known whether this sex difference would be found in older cohorts or those with established lung or cardiovascular disease: most previous reports on associations between endothelial function and respiratory diseases comprise relatively smaller samples of older men and women and, as far as we are aware, none have investigated sex differences. We can only speculate on the reasons for this effect modification by sex. There are established, but poorly understood, sex differences in the associations between lung function and other systemic conditions: previous research in this cohort has identified several sex interactions between lung function and non-respiratory health. For example, we have found that obesity and gastro-oesophageal reflux are associated with airflow obstruction among women, but not among men. On the other hand, adiposity and cardiorespiratory fitness are more strongly associated with lung volumes in boys and men than girls and women.

Endothelial function is regulated differently in men and women, with a strong influence of sex hormones. Although women generally have better endothelial

Figure 2 Scatterplots of endothelial function (FRHI) and spirometry values for FEV1, FVC and FEV1/FVC ratio. Values for women are indicated by crosses and dashed lines. Values for men are indicated by dots and solid lines. Standardized beta coefficients and P-values are from unadjusted linear regression analyses. FEV1, forced expiratory volume in 1 s; FRHI, Framingham reactive hyperaemia index; FVC, forced vital capacity.
function than men, cardiovascular risk factors (blood pressure, poor fitness and metabolic syndrome) are more strongly associated with endothelial function in healthy women without respiratory disease than men. Endothelial function was more strongly associated with High-Density Lipoprotein (HDL) cholesterol among women in the Framingham Heart Study, although it was more strongly correlated with BMI in men. Obstructive sleep apnoea is associated with reactive hyperaemic indices in women but not in men, and occupational stress has also been found to be more strongly associated with endothelial dysfunction in women than in men. Oestrogens are known to influence endothelial function and, because of the observed sex differences, we undertook additional post hoc analyses to explore whether blood oestradiol levels influenced the association of lung and endothelial function in women, but adjusting the analyses for oestradiol made no material difference to the observed associations.

The findings are consistent with previous studies that found associations between endothelial dysfunction and the severity of airflow obstruction among older smokers with and without COPD. Our study extends these observations to a younger cohort of people and show that the associations are independent of smoking. We also found a non-significant tendency to impaired endothelial function among participants with asthma, lending some support to an earlier observation. The lack of association between endothelial function and gas transfer (TLCO or TLCO/VA) in either sex contrasts with the findings from the EMCAP study of former smokers, among whom there were marginal associations between endothelial dysfunction and impaired gas transfer and significant associations with emphysema on computed tomography (CT) scan. Associations have also been shown between circulating endothelial microparticles, indicating apoptosis, and both emphysema and lower gas transfer in participants with COPD. In the EMCAP study, the association between gas transfer and endothelial function was not significant among former smokers without COPD, so it may be too early to detect associations between gas transfer and endothelial function in our cohort who are unlikely to have developed clinically significant emphysema by age 38 years.

The strengths of this analysis include the use of a population-based sample with a high rate of participation. The cohort design avoids confounding by age and we were able to adjust for asthma diagnoses and lifetime exposure to tobacco smoking. We also controlled for potential confounding by systemic inflammation, fitness and BMI, which are associated with both lung and endothelial function in this cohort, and we conducted sensitivity analyses after excluding participants with asthma and other diseases that may plausibly influence lung and endothelial function. A limitation is that the cohort is too young for many participants to have developed clinically significant emphysema.

### Table 3 Regression analyses of associations between endothelial function and lung function with multiple adjustments

<table>
<thead>
<tr>
<th>Main predictor</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Coefficient (95% Cl)</td>
</tr>
<tr>
<td>FEV₁ (L)</td>
<td>418</td>
<td>0.18 (0.09 to 0.28)</td>
</tr>
<tr>
<td>FVC (L)</td>
<td>418</td>
<td>0.09 (0.01 to 0.17)</td>
</tr>
<tr>
<td>FEV₁/FVC ratio</td>
<td>418</td>
<td>0.72 (0.13 to 1.31)</td>
</tr>
<tr>
<td>TLC (L)</td>
<td>418</td>
<td>0.06 (0.00 to 0.13)</td>
</tr>
<tr>
<td>FRC (L)</td>
<td>418</td>
<td>0.10 (0.02 to 0.19)</td>
</tr>
<tr>
<td>RV (L)</td>
<td>418</td>
<td>0.06 (−0.06 to 0.17)</td>
</tr>
<tr>
<td>sGaw (mL/s/cm H₂O/L)</td>
<td>418</td>
<td>0.81 (0.04 to 1.58)</td>
</tr>
<tr>
<td>TLCO (mmol/min/kPa/L)</td>
<td>408</td>
<td>0.007 (−0.008 to 0.021)</td>
</tr>
<tr>
<td>TLCO/VA (mmol/min/kPa/L)</td>
<td>408</td>
<td>−0.031 (0.097 to 0.035)</td>
</tr>
</tbody>
</table>

Analyses by linear regression using Framingham reactive hyperaemia index as the dependent variable and measures of lung function as the main predictors. Coefficients represent the difference in Framingham reactive hyperaemia index associated with unit differences in measures of lung function. Beta coefficients represent the SD (z-score) differences in Framingham reactive hyperaemia index associated with SD differences in measures of lung function. All analyses are adjusted for height, BMI, log C-reactive protein, V’O₂max, pack-years smoking and current asthma. Analyses using TLCO and TLCO/VA are also adjusted for exhaled carbon monoxide and haemoglobin.

BMI, body mass index; FEV₁, forced expiratory volume in 1 s; FRC, functional residual capacity; FVC, forced vital capacity; RV, residual volume; sGaw, specific airway conductance adjusted for thoracic gas volume; TLC, total lung capacity; TLCO, transfer factor for carbon monoxide; alveolar volume; V’O₂max, maximum oxygen uptake at peak exercise.

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Future studies should explore sex differences in endothelial function in patients with established COPD and longitudinal research is needed to understand how these preclinical associations evolve to impact health.

In summary, airflow obstruction and lower lung function are associated with lower endothelial function independently of smoking among early middle-aged women, but associations among men are weaker and less convincing. Research into the influence of endothelial function on respiratory and cardiovascular disease should investigate the possible sex differences.

Data availability statement

The Dunedin Multidisciplinary Health and Development Study does not have permission from the participants or ethical approval to make the data publicly available. Please contact the corresponding author for further information.

Acknowledgements

The Dunedin Multidisciplinary Health and Development Study is supported by the Health Research Council of New Zealand and the New Zealand Ministry of Business, Innovation and Employment (MBIE). Additional funding was provided by Duke University (USA). We are grateful to the study members and their friends and families for their continued support. We thank the respiratory physiologists and interviewers who obtained the measurements. We also thank Professor Richie Poulton (University of Otago), the study director, Dr Phil A. Silva, the study founder, and Professors Terrie Moffitt and Avshalom Caspi (Duke University) for their support. M.R.S. holds the AstraZeneca chair in Respiratory Epidemiology at McMaster University.

Abbreviations: COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; FEV1, forced expiratory volume in 1 s; FRC, functional residual capacity; FRHI, Framingham reactive hyperaemia index; FVC, forced vital capacity; IQR, interquartile range; RHc, reactive hyperaemia in the control arm; RHo, reactive hyperaemia in the occluded arm; RV, residual volume; sGaw, specific airway conductance adjusted for thoracic gas volume; TlC, total lung capacity; TlCO, transfer factor for carbon monoxide; V̇O2max, maximum oxygen uptake at peak exercise; VA, alveolar volume.

REFERENCES


Supplementary Information
Additional supplementary information can be accessed via the html version of this article at the publisher’s website.

Appendix S1 Methods.
Table S1 Participants reporting asthma or past year asthma treatment, pregnant women and participants not undertaking endothelial function tests or any measure of lung function are excluded. Pack-years analysis restricted to participants who have ever smoked.
Table S2 Height-adjusted regression analyses of associations between endothelial function and lung function among non-asthmatics.
Table S3 Regression analyses of associations between endothelial function and lung function with multiple adjustments and excluding participants with asthma, diabetes, cancer, heart disease and arthritis.
Table S4 Regression analyses of associations between endothelial function and post-bronchodilator spirometry with multiple adjustments.