Midlife Respiratory Function Related to White Matter Lesions and Lacunar Infarcts in Late Life
The Prospective Population Study of Women in Gothenburg, Sweden

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Background and Purpose—Increased evidence suggests that poor respiratory function increases risk of ischemic damage to the brain. Longitudinal studies on respiratory function and cerebral small-vessel disease are lacking. We examined midlife and late-life respiratory function in relation to small-vessel disease on computed tomography (CT) in women followed for 26 years.

Methods—White matter lesions (WMLs) and lacunar infarcts were rated on brain CT scans in 2000 in 379 women 70 to 92 years of age from a longitudinal population study in Göteborg, Sweden. Respiratory function was measured by peak expiratory flow (PEF) in 1974 and 2000 and by forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV₁) in 1980 and 2000.

Results—Lower FVC and FEV₁ in 1980 and 2000 were associated with presence and severity of WMLs and lacunar infarcts in 2000. Per 1-SD decrease of FVC in 1980, odds ratios (95% CIs) were 1.49 (1.11 to 2.02) for presence of WMLs and 1.95 (1.34 to 2.84) for lacunar infarcts after adjustment for potential confounders. Per 1-SD decrease of FEV₁ in 1980, adjusted odds ratios were 1.46 (1.06 to 2.00) for presence of WMLs and 1.42 (1.02 to 1.97) for lacunar infarcts. PEF in 1974 and 2000 was not associated with WMLs or lacunar infarcts.

Conclusions—WMLs and lacunar infarcts in elderly women were related to lower midlife respiratory function. Although our data may not establish causation between lower respiratory function and small-vessel disease, they imply the importance of good respiratory function in midlife.

Key Words: lacunar infarction ■ respiratory function tests ■ leukoaraiosis

Cerebral white matter lesions (WMLs) and lacunar infarcts are common findings on computed tomography (CT) and MRI in the elderly. They have been related to dementia, cognitive decline, depression, stroke, and gait disorders. On histopathology, WMLs on CT are supposed to represent marked ischemic demyelination with arteriolosclerosis, hyalinosis, and narrowing of the lumen of the small penetrating arteries in the white matter. Lacunar infarcts are small infarcts in the basal ganglia, thalamus, internal capsule, corona radiata, and brain stem, resulting from occlusions of penetrating arteries by atheroma or lipohyalinosis. Older age and hypertension have consistently been reported as risk factors for these brain lesions.

It has been suggested that hypoperfusion and ischemia may be involved in the pathogenesis of WMLs and lacunar infarcts. Experimental study found that hypoxia exacerbates effects of ischemia. Lower respiratory function may thus increase the risk for small-vessel disease by lowering oxygen supply to the brain. Furthermore, lower respiratory function increases inflammatory responses in blood vessels, which may lead to atherosclerosis. Cross-sectional studies have found associations between lower respiratory function and WMLs and lacunar infarcts, but studies with long follow-ups are lacking. We therefore investigated the relationship between midlife respiratory function and WMLs and lacunar infarcts on CT in a population-based sample of women followed for 26 years.

Methods

Participants
The study is part of the Prospective Population Study of Women in Gothenburg, which was initiated in 1968 to 1969 with an examination of 1462 women (participation rate 90%) born in 1908, 1914, 1918, 1922, and 1930. Participants were systematically sampled from the census register based on birth dates. The women were re-examined in 1974 to 1975, 1980 to 1981, 1992 to 1993, and 2000.

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to 2001. In 1980 to 1981, 47 women born 1930 were invited to participate for the first time.

All 1002 women surviving to September 1, 2000, were eligible for the 2000 to 2001 follow-up. However, 47 women died before they could be examined, and 20 had emigrated outside Sweden, leaving an effective sample of 935, among whom 684 agreed to participate. All 684 participants were invited for a CT scan of the brain, and 379 accepted (55.4% of those invited to CT; 40.5% of the effective sample). Compared with eligible nonparticipants, participants in the CT study were younger, less often smokers, less often hypertensive, and had higher peak expiratory flow (PEF), forced vital capacity (FVC), and forced expiratory volume in 1 second (FEV₁) in 1974 and 1980. Compared with other 2000 participants, those in the CT study were younger and had less heart disease, a higher level of physical activity, lower body mass index (BMI), and higher PEF, FVC, and FEV₁ in 2000.

Respiratory function tests were performed in 1974, 1980, and 2000. Among those with a CT in 2000, 360 had PEF in 1974; 359 had FVC and FEV₁ in 1980, 350 had PEF and 126 (only women born in 1930) had FVC and FEV₁ in 2000. Table 1 shows the number of participants with respiratory function at each examination by birth cohort. The study was approved by the ethics committee of Göteborg University. All participants gave informed consent to participate in accordance with the provisions of the Helsinki Declaration.

Assessment of Respiratory Function
Respiratory function tests were performed by experienced nurses. PEF was measured by peak flowmeter in 1974 and 2000. Participates were asked to exhale with a maximally forced effort from a position of maximal inspiration. Each participant performed the PEF test 3 times, and the highest value was used in both examinations. FVC and FEV₁ were measured by spirometry in 1980 and 2000. Participants were asked to inhale to total lung capacity before beginning the forced expiration with maximum effort throughout the expiration. In 1980, each participant performed the test twice, and the second value was used. In 2000, each participant performed the test 3 times, and the highest value was used.

CT Scans of the Brain
All CT scans were performed without contrast enhancement and with 8-mm continuous slices. The scans were examined by a neurologist experienced in visual rating scales and blinded to the participants' clinical characteristics. Intraobserver reliability was tested in 50 participants. Observed agreement was 82% (κ 0.65) for WMLs and 76% (κ 0.52) for presence of lacunar infarcts.

WMLs were defined as low-density areas in the periventricular white matter. Decreased density was rated as no, mild, moderate, and severe in relation to the attenuation of normal white matter.1

Lacunar infarcts were defined as round or oval lesions, 5 to 15 mm in diameter, in the territory supplied by deep or superficial small perforating arteries. Lesions were not in cortical territories and were without morphological and topographic distributions consistent with internal watershed zone infarcts.19

### TABLE 1. No. of Participants at Each Examination

<table>
<thead>
<tr>
<th>Birth year</th>
<th>PEF 1974 Age (n)</th>
<th>FVC and FEV₁ 1980 Age (n)</th>
<th>PEF 2000 Age (n)</th>
<th>FVC and FEV₁ 2000 Age (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1930</td>
<td>44 (158)</td>
<td>50 (165)</td>
<td>70 (163)</td>
<td>70 (126)</td>
</tr>
<tr>
<td>1922</td>
<td>52 (104)</td>
<td>58 (100)</td>
<td>78 (100)</td>
<td></td>
</tr>
<tr>
<td>1918</td>
<td>56 (77)</td>
<td>62 (73)</td>
<td>82 (70)</td>
<td></td>
</tr>
<tr>
<td>1914</td>
<td>60 (19)</td>
<td>66 (19)</td>
<td>86 (15)</td>
<td></td>
</tr>
<tr>
<td>1908</td>
<td>66 (2)</td>
<td>72 (2)</td>
<td>92 (2)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>360</td>
<td>359</td>
<td>350</td>
<td>126</td>
</tr>
</tbody>
</table>

Assessments of Potential Confounders
At each examination, information on smoking, physical activity, asthma, chronic bronchitis, myocardial infarction, and angina pectoris was obtained by interviews according to a standardized questionnaire. Blood samples were taken after overnight fast, and serum cholesterol concentration was measured. Blood pressure was measured in the sitting position after 5 minutes of rest. Body height was measured to the nearest centimeter and weight to the nearest 0.1 kg. Information on incident disorders was also obtained from the Swedish Hospital Discharge Register.

Smoking was classified as never, ex-smokers, and current. The levels of physical activity at leisure time were rated as low, medium (≥4 hours of light physical activity per week), and high (regularly more rigorous or heavy physical activity). Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or taking antihypertensive medication. BMI was calculated as kg/m².

Statistical Analysis
Independent sample t tests or χ² tests were used to compare CT participants and nonparticipants. Logistic regression models were used to assess the association between respiratory function and presence of WMLs and lacunar infarcts. Ordinal regression models were used to test associations between respiratory function and severity of WMLs and number of lacunar infarcts. Associations were presented as odds ratios (ORs) and 95% CIs after adjustment for multiple potential confounders. Concurrent confounders (collected in the same examination as each respiratory function test) were age, height, smoking, physical activity, BMI, pulmonary disease, heart disease, hypertension, and cholesterol. Incident confounders during follow-up included incident heart disease, hypertension, diabetes mellitus, pulmonary diseases, and change in BMI.

To test potential modifying effects of smoking, physical activity, hypertension, heart disease, and BMI on the relationship between respiratory function and brain lesions, interaction terms for respiratory function by smoking (never versus former–current), physical activity (low versus medium–high), hypertension, heart disease, and BMI were examined.

Results
Characteristics of the study sample in each examination are presented in Table 2. Among 360 participants in 1974, 209 (58%) had WMLs (148 mild, 38 moderate, and 23 severe), 135 (38%) had lacunar infarcts (86 had 1, and 49 ≥2), and 12 (3%) had cortical, watershed, or border zone infarcts on brain CT scans in 2000. Twenty-one women (6%) developed stroke, and 20 (6%) developed transient ischemic attack between 1974 and 2000.

Table 3 presents mean values and SDs of respiratory function in 1974, 1980, and 2000 by severity of WMLs and number of lacunar infarcts in 2000. After adjustments for age, lower FVC and FEV₁ in 1980 were associated with severity of WMLs. Lower FVC and FEV₁ in 1980 were associated with number of lacunar infarcts.

Table 4 presents odds of WMLs and lacunar infarcts per 1-SD decrease in respiratory function. Lower FVC and FEV₁ in 1980 were associated with presence and severity of WMLs, as well as presence and number of lacunar infarcts in 2000 after adjustment for baseline age, height, BMI, physical activity, smoking, lung disease, heart disease, hypertension, and cholesterol in 1980 and incident lung disease, heart disease, diabetes mellitus, and hypertension and changes of BMI from 1980 to 2000. Per 1-SD decrease in FVC in 1980, multivariate-adjusted ORs (95% CIs) were 1.49 (1.11 to 2.02) for presence of WMLs and 1.95 (1.34 to 2.84) for lacunar infarcts. Per 1-SD decrease in FEV₁ in 1980, multivariate-adjusted ORs were 1.46 (1.06 to
2.00) for presence of WMLs and 1.42 (1.02 to 1.97) for lacunar infarcts. Lower FVC and FEV1 in 2000 were cross-sectionally associated with presence and severity of WMLs and lacunar infarcts in 2000. PEF in 1974 and 2000 was not associated with WMLs and lacunar infarcts.

There is no interaction between respiratory function and smoking, physical activity, hypertension, heart disease, and BMI in relation to WMLs and lacunar infarcts. Associations between respiratory function and brain lesions remained after excluding 39 women with stroke or transient ischemic attack or other infarcts on CT (cortical, watershed, and border zone infarct). Change in PEF from 1974 to 2000 (n = 334) and changes in FVC and FEV1 from 1980 to 2000 (n = 121) were not related to presence of WMLs and lacunar infarcts.

**Discussion**

To our knowledge, this is the first prospective study on midlife respiratory function in relation to WMLs and lacunar infarcts in late life. We found that presence and severity of WMLs and lacunar infarcts on CT in 2000 were associated with lower respiratory function measured 20 years earlier, after adjustment for multiple potential confounders. We also found cross-sectional associations between respiratory function and WMLs and lacunar infarcts in 2000. Our findings are supported by 3 cross-sectional MRI studies.15–17 Study findings suggest that lower respiratory function in midlife may increase risk of cerebral small-vessel disease in late life.

There are possible biological mechanisms that might explain our results. First, hypoxia exacerbates the effects of ischemia in rat models.13 Lower respiratory function may thus increase vulnerability for small-vessel disease by lowering oxygen supply to the brain. In support of this, a previous study reported that hypoxemia, even very mild, was associated with periventricular WMLs on MRI.20 Second, lower respiratory function is associated with higher levels of fibrinogen and other inflammation-sensitive plasma proteins that may increase the risks of atherosclerosis and cardiovascular diseases.14 Third, lower respiratory function may cause blood–brain barrier disturbance through chronic hypoxia and ischemia.21 Disturbed blood–brain barrier was associated with WMLs11–12,22 and lacunar infarcts.22 Lower respiratory function has been associated with coronary heart disease,23 stroke,24 hypertension,25 and higher BMI.


<table>
<thead>
<tr>
<th>WMLs in 2000</th>
<th>PEF 1974 (L/min)</th>
<th>FVC 1980 (L)</th>
<th>FEV1, 1980 (L)</th>
<th>PEF 2000 (L/min)</th>
<th>FVC 2000 (L)</th>
<th>FEV1, 2000 (L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>151</td>
<td>447±72</td>
<td>3.6±0.6</td>
<td>155</td>
<td>2.9±0.5</td>
<td>71</td>
</tr>
<tr>
<td>Mild</td>
<td>148</td>
<td>431±70</td>
<td>3.4±0.5</td>
<td>147</td>
<td>2.7±0.5</td>
<td>150</td>
</tr>
<tr>
<td>Moderate</td>
<td>38</td>
<td>441±68</td>
<td>3.3±0.5</td>
<td>35</td>
<td>2.6±0.4</td>
<td>36</td>
</tr>
<tr>
<td>Severe</td>
<td>23</td>
<td>424±73</td>
<td>3.1±0.6</td>
<td>22</td>
<td>2.5±0.5</td>
<td>18</td>
</tr>
<tr>
<td>*P for trend</td>
<td>P=0.855</td>
<td>P=0.006</td>
<td>P=0.015</td>
<td>P=0.039</td>
<td>P=0.005</td>
<td>P=0.005</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No. of lacunar infarcts in 2000</th>
<th>PEF 1974 (L/min)</th>
<th>FVC 1980 (L)</th>
<th>FEV1, 1980 (L)</th>
<th>PEF 2000 (L/min)</th>
<th>FVC 2000 (L)</th>
<th>FEV1, 2000 (L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>225</td>
<td>444±66</td>
<td>3.5±0.6</td>
<td>229</td>
<td>2.8±0.5</td>
<td>219</td>
</tr>
<tr>
<td>1</td>
<td>86</td>
<td>434±72</td>
<td>3.3±0.6</td>
<td>84</td>
<td>2.6±0.5</td>
<td>70</td>
</tr>
<tr>
<td>≥2</td>
<td>49</td>
<td>417±88</td>
<td>3.2±0.5</td>
<td>46</td>
<td>2.6±0.5</td>
<td>47</td>
</tr>
<tr>
<td>*P for trend</td>
<td>P=0.110</td>
<td>P=0.001</td>
<td>P=0.008</td>
<td>P=0.168</td>
<td>P=0.231</td>
<td>P=0.444</td>
</tr>
</tbody>
</table>

*P for trend adjusted by age (P for FVC 2000 and FEV1, 2000 were not age adjusted because all individuals were 70 years of age).
and cholesterol.26 However, in our study, the associations between lower respiratory function and WMLs and lacunar infarcts did not change after controlling for these factors. No vascular factors made independent contributions to the risk of small-vessel disease. The reason for this may be that participants in the CT study were healthier than the rest of the population. Associations between lower respiratory function and small-vessel disease were thus not mediated by these vascular factors in our study.

Among the strengths of this study are the long duration of follow-up and population-based study sample. However, several methodological issues need to be considered. First, atrition attributable to refusal and loss to follow-up is a problem of long-term prospective studies. In our study, only 40.5% of the eligible sample participated in the CT scan. CT participants were younger, had heart disease less often, and had a higher level of physical activity and higher respiratory function than nonparticipants. Therefore, a healthy participant effect may underestimate the real association between respiratory function and small-vessel disease. Second, no men were enrolled in this study, therefore, we cannot comment on the significance of these findings in men. Men have fewer WMLs and lacunar infarcts2,15 and higher respiratory function than women. Thus, studies in men are needed. Third, FVC and FEV₁ are less variable and less effort dependent than PEF27 and therefore more accurate measures of respiratory function. This may be 1 reason why FVC and FEV₁ were consistently associated with WMLs and lacunar infarcts in both cross-sectional and longitudinal analyses, whereas PEF was not. Fourth, CT scans are less sensitive than MRI in detecting WMLs. However, the high sensitivity of MRI may reveal WMLs that are not clinically relevant. A previous study suggested that WMLs on CT better predicted later development of symptomatic cerebrovascular diseases than WMLs noted on MRI, supporting the view that CT may be more specific.28 Fifth, enlarged perivascular space may be misclassified as small lacunar infarcts. We therefore defined lacunar infarcts as a diameter >5 mm in this study. However, misclassification may still exist given that the margins of some lesions are not clearly defined on CT. Finally, CT scans were not conducted at the baseline examinations in 1974 and 1980. Thus, it is, possible that some women might have had these brain changes already at baseline. However, considering that most women were healthy and young at that time, the frequency of small-vessel disease was likely low.

In conclusion, we found that lower respiratory function in midlife was associated with WMLs and lacunar infarcts detected on CT in late life. This study was based on a general population, and 99% of participants had normal respiratory function defined by the European Respiratory Society.29 However, respiratory function varies widely even in healthy individuals.30 Intervention studies show that physical exercise improves PEF and oxygen uptake in healthy people.31–32 Although our data may not establish causation between lower respiratory function and small-vessel disease, they imply the importance of good respiratory function in midlife.

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**Disclosures**

None.

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