Orosomucoid, Carotid Plaque, and Incidence of Stroke

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Background and Purpose—Orosomucoid (α-1-acid glycoprotein) is an acute-phase protein that has been implicated in anti-inflammatory, immunomodulating, and angiogenic pathways. Orosomucoid has also been associated with coronary disease and stroke. The relationship between orosomucoid, carotid plaque, and stroke incidence were explored in this study.

Methods—Plasma levels of orosomucoid were assessed in 4285 subjects (39.8% men; mean age 57.5±5.9 years) without cardiovascular disease, who participated in the Malmö Diet and Cancer Study, between 1991 and 1994. The right carotid artery was examined for plaque using B-mode ultrasound examination. Incidence of stroke was followed up during a median follow-up time of 17.7 years.

Results—Carotid plaque was present in 43.5% at baseline. Orosomucoid was significantly higher in subjects with carotid plaque (mean±SD: 0.72±0.22 versus 0.69±0.20 g/L; P<0.001). A total of 234 subjects were diagnosed with ischemic stroke during follow-up. Orosomucoid was associated with ischemic stroke after adjustment for risk factors, with hazard ratio 1.48 (95% confidence interval, 1.02–2.16) comparing the third versus first tertile. In subjects with plaque and belonging to the top tertile of orosomucoid, the hazard ratio was 2.07 (95% confidence interval, 1.38–3.11) compared with those without plaque and with orosomucoid in the first and second tertiles, after adjustment for C-reactive protein and other risk factors.

Conclusions—Elevated levels of orosomucoid are associated with increased occurrence of carotid plaque and increased incidence of ischemic stroke. The combination of high orosomucoid and carotid plaque substantially increase the risk of stroke. (Stroke. 2016;47:1858-1863. DOI: 10.1161/STROKEAHA.116.013374.)

Key Words: acute-phase reaction ■ carotid artery disease ■ cytokines ■ risk factor ■ stroke

α-1-acid glycoprotein or orosomucoid was first described in 1950 and is an acute-phase protein mainly synthesized in the liver, but also in extrahepatic sites. The plasma concentrations of orosomucoid raise several fold in response to acute inflammation. The function of orosomucoid is still incompletely known, but it is believed that orosomucoid modulates the immune system in the acute-phase reaction. Inflammatory cytokines, such as interleukin 1 and tumor necrosis factor-α, can stimulate production of orosomucoid by leukocytes, and it has been proposed that orosomucoid is part of a negative feedback system. Several studies have also reported complex relationships between orosomucoid and angiogenesis in response to vascular injury in animal experiments. Orosomucoid produced by endothelial cells has been shown to induce angiogenesis and enhance endothelial cell migration and capillary tube formation in vitro.

The anti-inflammatory, immunomodulating, and angiogenic effects of orosomucoid could be of importance for the pathogenesis of cardiovascular disease. Elevated plasma levels of orosomucoid have been associated with coronary disease and stroke in men. However, studies are scarce, and to our best knowledge, no study has investigated the relationship between orosomucoid and stroke in women. Orosomucoid has also been associated with carotid atherosclerosis, which is a major stroke risk factor and a source of thromboembolism leading to stroke.

The purpose of this study was to examine the association between orosomucoid and carotid plaque in a population-based cohort of men and women and to study whether elevated levels of orosomucoid modify the relationship between carotid plaque and stroke.

Study Population

Between 1991 and 1996, citizens in Malmö, born between 1926 and 1945, were invited to participate in the Malmö Diet and Cancer Study. A total of 28,449 subjects (60% women) participated. Of those, a random sample of 6103 subjects, who entered the Malmö Diet and Cancer Study between 1991 and 1994, were selected to participate in a study of the epidemiology of carotid artery diseases.
of whom 5540 subjects donated fasting blood samples. Complete information about orosomucoid and high-sensitive c-reactive protein (hsCRP) was available for 4891 subjects. Participants with previous stroke at baseline (n=36), missing information regarding carotid plaque (n=187), low-density lipoprotein (n=125), cystatin C (n=240), body mass index (n=4), or diabetes mellitus (n=14) were excluded. After exclusions, 4285 subjects remained. The ethical committee at Lund University approved the Malmö Diet and Cancer Study. All participants provided informed consent.

A self-administered questionnaire was used to obtain information about smoking habits, history of diabetes mellitus, and the use of antidiabetic drugs, blood pressure–lowering drugs, or lipid-lowering drugs. Smoking was categorized into never smokers, former smokers, and current smokers (those who smoked regularly or occasionally). Blood pressure was measured in the supine position after 10 minutes of rest. Height was measured to the nearest centimeter and weight to the nearest kilogram as previously described. Body mass index was calculated as weight in kilograms divided by squared height in meters (kg/m²). Diabetes mellitus was defined as self-reported physician diagnosis or treatment with antidiabetic medication or a fasting whole blood glucose level ≥ 6.1 mmol/L (corresponding to plasma glucose of 7.0 mmol/L).

B-mode ultrasonography (Acuson 128 CT System, Mountain View, CA) examination of the right carotid artery was performed by trained, certified sonographers as described. The carotid artery was examined and imaged for the presence of atherosclerotic plaque, defined as a focal thickening of the intima–media layer >1.2 mm. Fasting cholesterol and glucose levels were analyzed on fresh blood samples according to standard procedures at the Department of Clinical Chemistry, University Hospital Malmö. Low-density lipoprotein levels were calculated according to the Friedewald formula.

Venous blood samples were taken in the morning after fasting overnight and frozen at −80°C immediately after collection. Plasma orosomucoid was analyzed in 2013, from frozen EDTA plasma, using an immunoturbidimetric assay on the Cobas c-system (Roche Diagnostics, Germany). The reference value was 0.5 to 1.2 g/L, and the lower limit of detection was 0.1 g/L. Mean inter- and intra-assay coefficients of variation were 1.5% and 0.7%, respectively, for orosomucoid. Plasma levels of hsCRP were analyzed in 2002 using the Tina-quant CRP latex high-sensitivity assay (Roche Diagnostics, Basel, Switzerland) on an ADVIA 1650 Chemistry System (Bayer Healthcare, NY). Cystatin C was measured in 2008 using a particle-enhanced immunonephelometric assay (N Latex Cystatin; Siemens Healthcare, NY). The reference value was 0.5 to 1.2 g/L, and the lower limit of detection was 0.1 g/L. Mean interassay coefficients of variation were 4.3% for Cystatin C. A Cystatin C Equation (CKD-EPI 2012) was used to calculate estimated glomerular filtration rate.

Follow-Up
All subjects were followed up from the baseline examination until first onset of stroke, emigration from Sweden, death, or end of follow-up at December 31, 2010. Incident ischemic stroke was ascertained by linkage to the Stroke Register of Malmö, which included validation of the diagnosis by review of hospital records. Stroke cases who moved out from the city of Malmö were identified from the Swedish Hospital Discharge Register. Case retrieval and methods of defining ischemic stroke has been described before.

Statistics
HsCRP was positively skewed and therefore log normalized. The distribution of orosomucoid levels in the study population are presented in Figure 1. Subjects were categorized into sex-specific tertiles on the basis of orosomucoid concentrations. Subjects with and without plaque were compared using Student t test for continuous variables and χ² test for dichotomous variables. The results were presented as means±SD, median with interquartile range, or percentages as appropriate. A general linear model was used to compare orosomucoid levels in subjects with and without plaque, after adjustments for risk factors. Cox proportional hazards regression was used to compare incidence of ischemic stroke in relation to orosomucoid and to calculate hazard ratios (HR) in 3 separate models adjusted for (1) age and sex; (2) model 1+smoking status, systolic blood pressure, blood pressure medication, diabetes mellitus, low-density lipoprotein, lipid-lowering medication, body mass index, estimated glomerular filtration rate; and (3) model 2+hsCRP. We also evaluated the joint effect of orosomucoid and carotid plaque by dividing the cohort into 4 groups according to orosomucoid (top tertile versus first or second tertile) and plaque (yes versus no). Potential interactions between orosomucoid and carotid plaque were analyzed by including a multiplicative interaction term in the final model. All analyses were performed using STATA version 12.1 and IBM SPSS Statistics version 22.0. Two-tailed P<0.05 was considered statistically significant.

Results
Baseline characteristics in individuals with and without plaque are presented in Table 1. Mean orosomucoid (in g/L)
Orosomucoid and Carotid Plaque
Carotid plaque was associated with increased concentrations of orosomucoid (0.72±0.22 g/L versus 0.69±0.20 g/L; \( P < 0.001 \) for those with and without plaque). After adjustment for risk factors (age, sex, systolic blood pressure, low-density lipoprotein, diabetes mellitus, current smoking, body mass index, renal function, blood pressure medication, and hsCRP), orosomucoid remained significantly higher in subjects with carotid plaque (adjusted mean values: 0.711 g/L [95% confidence interval (CI), 0.703–0.720] versus 0.696 g/L [95% CI, 0.689–0.704]; \( P = 0.010 \)).

Incidence of Stroke
During a median follow-up of 17.7 years, a total of 276 subjects were diagnosed with new-onset stroke, of which 234 were ischemic. The incidence of stroke in relation to tertiles of orosomucoid is presented in Table 2.

Adjusted for age and sex, orosomucoid was significantly associated with ischemic stroke, HR: 2.13 (95% CI, 1.53–2.98) for the highest tertile compared with the lowest. This association remained significant (HR: 1.48; 95% CI, 1.02–2.16) after adjustment for risk factors, including hsCRP. The HR per 1 SD increment of orosomucoid was 1.34 (CI, 1.21–1.49; \( P < 0.001 \)) for model 1 and 1.19 (CI, 1.04–1.36; \( P = 0.012 \)) after adjustments in model 3. In a subgroup analysis (Table 3), orosomucoid was associated with ischemic stroke both in men and women when adjusted for risk factors (model 2), HR: 1.30 (95% CI, 1.10–1.52) in women and HR: 1.24 (95% CI, 1.06–1.46) in men. When additional adjustment was made for hsCRP, the association remained significant for women only, HR: 1.26 (95% CI, 1.05–1.52) versus HR: 1.12 (95% CI, 0.91–1.37).

Joint Effects of Orosomucoid and Carotid Plaque
Subjects with carotid plaque and levels of orosomucoid in the top tertile had a substantially increased risk for stroke compared with those without carotid plaque and levels of orosomucoid in the first or second tertile. The age- and sex-adjusted HR was 2.62 (95% CI, 1.86–3.69) and 1.80 (95% CI, 1.24–2.61) after full adjustments for risk factors and hsCRP. For ischemic stroke, the corresponding HRs was 3.04 (95% CI, 2.09–4.41) and 2.07 (95% CI, 1.38–3.11), respectively (Table 4 and Figure 2). There was no significant multiplicative

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### Table 1. Baseline Characteristics of Subjects With and Without Carotid Plaque

<table>
<thead>
<tr>
<th></th>
<th>No Carotid Plaque</th>
<th>Carotid Plaque</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=2420)</td>
<td>(n=1865; 43.5%)</td>
</tr>
<tr>
<td>Men, %</td>
<td>36.5</td>
<td>44.1</td>
</tr>
<tr>
<td>( P ) Value</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>56.2±5.9</td>
<td>59.3±5.5</td>
</tr>
<tr>
<td>( P &lt; 0.001 )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.6±3.8</td>
<td>25.5±3.8</td>
</tr>
<tr>
<td>( P = 0.294 )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BP medication</td>
<td>12.4</td>
<td>19.8</td>
</tr>
<tr>
<td>( P &lt; 0.001 )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>6.6</td>
<td>8.9</td>
</tr>
<tr>
<td>( P = 0.004 )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL, mmol/L</td>
<td>4.04±0.98</td>
<td>4.31±0.98</td>
</tr>
<tr>
<td>( P &lt; 0.001 )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipid-lowering medication</td>
<td>1.2</td>
<td>3.6</td>
</tr>
<tr>
<td>( P &lt; 0.001 )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current/former smoking</td>
<td>21.2/31.5</td>
<td>30.2/33.7</td>
</tr>
<tr>
<td>( P &lt; 0.001 )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>137.3±17.8</td>
<td>145.5±19.2</td>
</tr>
<tr>
<td>( P &lt; 0.001 )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>85.8±9.3</td>
<td>87.8±9.3</td>
</tr>
<tr>
<td>( P &lt; 0.001 )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orosomucoid, g/L</td>
<td>0.69±0.20</td>
<td>0.72±0.22</td>
</tr>
<tr>
<td>( P &lt; 0.001 )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>0.69±0.19</td>
<td>0.73±0.23</td>
</tr>
<tr>
<td>( P &lt; 0.001 )</td>
<td></td>
<td></td>
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<tr>
<td>Women</td>
<td>0.68±0.21</td>
<td>0.71±0.21</td>
</tr>
<tr>
<td>( P &lt; 0.001 )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>hsCRP, mg/L</td>
<td>1.2 (0.6–2.5)</td>
<td>1.4 (0.7–3.0)</td>
</tr>
<tr>
<td>( P &lt; 0.001 )</td>
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</tbody>
</table>

Baseline characteristics of 4285 individuals free of stroke at baseline are shown. For continuous traits, mean±SD are given for normally distributed traits and median (interquartile range) for right skewed traits. For categorical traits, % are given. BMI indicates body mass index; BP, blood pressure; hsCRP, high-sensitive c-reactive protein; and LDL, low-density lipoprotein.

was 0.71±0.21 in men and 0.70±0.21 in women. Mean age at screening was 57.6±6.0 years in men and 57.5±5.9 years in women.

**Orosomucoid and Carotid Plaque**

Carotid plaque was associated with increased concentrations of orosomucoid (0.72±0.22 g/L versus 0.69±0.20 g/L; \( P < 0.001 \) for those with and without plaque). After adjustment for risk factors (age, sex, systolic blood pressure, low-density lipoprotein, diabetes mellitus, current smoking, body mass index, renal function, blood pressure medication, and hsCRP), orosomucoid remained significantly higher in subjects with carotid plaque (adjusted mean values: 0.711 g/L [95% confidence interval (CI), 0.703–0.720] versus 0.696 g/L [95% CI, 0.689–0.704]; \( P = 0.010 \)).

### Table 2. HRs of Stroke and Sex-Specific Tertiles of Orosomucoid

<table>
<thead>
<tr>
<th></th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orosomucoid, g/L</td>
<td>0.50±0.08</td>
<td>0.66±0.05</td>
<td>0.92±0.17</td>
</tr>
<tr>
<td>( n=4285 )</td>
<td>1370</td>
<td>1381</td>
<td>1534</td>
</tr>
<tr>
<td>Total stroke</td>
<td>65</td>
<td>83</td>
<td>128</td>
</tr>
<tr>
<td>Model 1</td>
<td>1 (ref)</td>
<td>1.39 (0.99–1.94)</td>
<td>1.85 (1.37–2.50)</td>
</tr>
<tr>
<td></td>
<td>1.28 (1.16–1.42)</td>
<td>( P &lt; 0.001 )</td>
<td></td>
</tr>
<tr>
<td>Model 2</td>
<td>1 (ref)</td>
<td>1.21 (0.86–1.70)</td>
<td>1.51 (1.10–2.06)</td>
</tr>
<tr>
<td></td>
<td>1.20 (1.07–1.33)</td>
<td>( P = 0.001 )</td>
<td></td>
</tr>
<tr>
<td>Model 3</td>
<td>1 (ref)</td>
<td>1.14 (0.81–1.60)</td>
<td>1.29 (0.92–1.82)</td>
</tr>
<tr>
<td></td>
<td>1.13 (0.99–1.28)</td>
<td>( P = 0.072 )</td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>51</td>
<td>69</td>
<td>114</td>
</tr>
<tr>
<td>Model 1</td>
<td>1 (ref)</td>
<td>1.52 (1.05–2.20)</td>
<td>2.13 (1.53–2.98)</td>
</tr>
<tr>
<td></td>
<td>1.34 (1.21–1.49)</td>
<td>( P &lt; 0.001 )</td>
<td></td>
</tr>
<tr>
<td>Model 2</td>
<td>1 (ref)</td>
<td>1.32 (0.90–1.92)</td>
<td>1.72 (1.22–2.42)</td>
</tr>
<tr>
<td></td>
<td>1.25 (1.12–1.40)</td>
<td>( P &lt; 0.001 )</td>
<td></td>
</tr>
<tr>
<td>Model 3</td>
<td>1 (ref)</td>
<td>1.24 (0.85–1.81)</td>
<td>1.48 (1.02–2.16)</td>
</tr>
<tr>
<td></td>
<td>1.19 (1.04–1.36)</td>
<td>( P = 0.012 )</td>
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</tbody>
</table>

Model 1 hazard ratio adjusted for age and sex. Model 2 adjusted for model 1+systolic blood pressure, blood pressure medication, low-density lipoprotein, lipid-lowering medication, diabetes mellitus, smoking status, body mass index, and glomerular filtration rate. Model 3 adjusted for model 2+hsCRP. CI indicates confidence interval; HR, hazard ratio; and hsCRP, high-sensitive c-reactive protein.
Orosomucoid is an acute-phase protein which is believed to have immunomodulating and angiogenic effects. Orosomucoid has been associated with increased incidence of cardiovascular diseases. We investigated the relationship between orosomucoid, carotid plaque, and stroke. Orosomucoid was associated with increased occurrence of carotid plaque and with increased incidence of ischemic stroke. Incidence of ischemic stroke was substantially increased in subjects with both carotid plaque and elevated levels of orosomucoid. These results remained significant after adjustments for cardiovascular risk factors.

To the best of our knowledge, orosomucoid and the association with stroke have previously been investigated in men only. In our study, orosomucoid was associated with ischemic stroke in women, even after the adjustment for risk factors and hsCRP.

The function of orosomucoid remains incompletely understood, and we can only speculate about possible mechanisms. Inflammation has an important role in the development and progression of atherosclerosis and ischemia. Orosomucoid produced by endothelial cells has been associated with anti-inflammatory, immunomodulating, and anti-apoptotic effects during ischemic-perfusion injury in murine models. Orosomucoid also stimulates angiogenesis, but the proangiogenic actions depend on other factors that modify the angiogenic effects. Hence, orosomucoid could be involved in compensatory and protective mechanisms and produced as a response to inflammation and vessel injuries. Orosomucoid in high concentrations has also been shown to inhibit platelet aggregation, which contextually would be protective against ischemic stroke. However, other studies of human platelets have shown that orosomucoid could induce alterations in platelet shape and possibly contribute to platelet activation, which hypothetically could increase the risk of ischemic stroke.

Ischemic stroke is a heterogeneous disease. Large artery atherosclerosis, such as carotid plaque, is an established risk factor for cerebral infarction. The role of orosomucoid in relation to carotid plaque burden is not known. However, in line with our study, a previous study reported elevated levels of orosomucoid in patients with carotid plaque. In our study, 9.3% (n=173) of subjects with carotid plaque had stroke, which is not insignificant. Carotid artery stenosis can be treated medically or with surgery, and the risk for stroke has been found low in subjects with asymptomatic stenosis on medical treatment. It is therefore important to study which patients with carotid plaque are at highest risk for ischemic stroke. Our results indicate that subjects with plaque and increased levels of orosomucoid might benefit from intensified risk factor treatment aimed at plaque stabilization to reduce the risk of ischemic stroke. Further studies are needed to investigate whether risk assessment in patients with plaque could be improved with the use of plasma biomarkers in addition to other risk factors.

The large prospective population-based cohort, a long follow-up time, and a relatively large number of stroke cases are needed to further investigate the role of orosomucoid in ischemic stroke.

### Table 3. Relationships Between Orosomucoid and Incidence of Stroke in Men and Women

<table>
<thead>
<tr>
<th></th>
<th>Men (n=1706)</th>
<th>Women (n=2579)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total stroke</td>
<td>128</td>
<td>148</td>
</tr>
<tr>
<td>Model 1</td>
<td>1.22 (1.04–1.41)</td>
<td>1.36 (1.18–1.56)</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.16 (0.99–1.37)</td>
<td>1.25 (1.07–1.46)</td>
</tr>
<tr>
<td>Model 3</td>
<td>1.07 (0.87–1.30)</td>
<td>1.18 (1.00–1.41)</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>113</td>
<td>121</td>
</tr>
<tr>
<td>Model 1</td>
<td>1.29 (1.11–1.50)</td>
<td>1.42 (1.22–1.64)</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.24 (1.06–1.46)</td>
<td>1.30 (1.10–1.52)</td>
</tr>
<tr>
<td>Model 3</td>
<td>1.12 (0.91–1.37)</td>
<td>1.26 (1.05–1.52)</td>
</tr>
</tbody>
</table>

Figures are hazards ratios (95% confidence intervals) per 1 SD increment of orosomucoid. Model 1 adjusted for age. Model 2 adjusted for model 1+systolic blood pressure, blood pressure medication, low-density lipoprotein, lipid-lowering medication, diabetes mellitus, smoking status, body mass index, and glomerular filtration rate. Model 3 adjusted for model 2+hsCRP. hsCRP indicates high-sensitive c-reactive protein.

### Discussion

The function of orosomucoid remains incompletely understood, and we can only speculate about possible mechanisms. Inflammation has an important role in the development and progression of atherosclerosis and ischemia. Orosomucoid produced by endothelial cells has been associated with anti-inflammatory, immunomodulating, and anti-apoptotic effects during ischemic-perfusion injury in murine models. Orosomucoid also stimulates angiogenesis, but the proangiogenic actions depend on other factors that modify the angiogenic effects. Hence, orosomucoid could be involved in compensatory and protective mechanisms and produced as a response to inflammation and vessel injuries. Orosomucoid in high concentrations has also been shown to inhibit platelet aggregation, which contextually would be protective against ischemic stroke. However, other studies of human platelets have shown that orosomucoid could induce alterations in platelet shape and possibly contribute to platelet activation, which hypothetically could increase the risk of ischemic stroke.

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The large prospective population-based cohort, a long follow-up time, and a relatively large number of stroke cases are needed to further investigate the role of orosomucoid in ischemic stroke.

### Table 4. Hazard Ratios of Stroke in Categories of High (Top Tertile) or Low (First and Second Tertile) Orosomucoid and Presence or Absence of Carotid Plaque

<table>
<thead>
<tr>
<th></th>
<th>Low Orosomucoid/No Plaque</th>
<th>High Orosomucoid/No Plaque</th>
<th>Low Orosomucoid/Plaque</th>
<th>High Orosomucoid/Plaque</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=4285</td>
<td>1557</td>
<td>760</td>
<td>1046</td>
<td>646</td>
</tr>
<tr>
<td>Total stroke, n</td>
<td>57</td>
<td>46</td>
<td>91</td>
<td>82</td>
</tr>
<tr>
<td>Model 1</td>
<td>1 (ref)</td>
<td>1.62 (1.10–2.39)</td>
<td>1.80 (1.28–2.51)</td>
<td>2.62 (1.86–3.69)</td>
</tr>
<tr>
<td>Model 2</td>
<td>1 (ref)</td>
<td>1.41 (0.95–2.10)</td>
<td>1.58 (1.12–2.22)</td>
<td>2.04 (1.43–2.92)</td>
</tr>
<tr>
<td>Model 3</td>
<td>1.25 (0.83–1.88)</td>
<td>1.57 (1.11–2.21)</td>
<td>1.80 (1.24–2.61)</td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke, n</td>
<td>45</td>
<td>38</td>
<td>75</td>
<td>76</td>
</tr>
<tr>
<td>Model 1</td>
<td>1 (ref)</td>
<td>1.70 (1.11–2.62)</td>
<td>1.85 (1.27–2.69)</td>
<td>3.04 (2.09–4.41)</td>
</tr>
<tr>
<td>Model 2</td>
<td>1 (ref)</td>
<td>1.47 (0.95–2.28)</td>
<td>1.63 (1.12–2.39)</td>
<td>2.36 (1.60–3.47)</td>
</tr>
<tr>
<td>Model 3</td>
<td>1.30 (0.83–2.05)</td>
<td>1.62 (1.11–2.37)</td>
<td>2.07 (1.38–3.11)</td>
<td></td>
</tr>
</tbody>
</table>
The lack of serial measurements to discover changes in plasma levels of biomarkers and risk factors over time is a limitation of our study. Indeed, raised orosomucoid levels are not only restricted to the acute-phase reaction but also in conditions such as rheumatoid arthritis, hepatitis, and different types of cancer. However, changes in orosomucoid levels over time would most likely bias the results toward null. In addition, previous studies of healthy individuals have shown that serum levels of orosomucoid are relatively stable with median intra- and interindividual coefficients of biological variation of 11.1% and 30.7%, respectively, for 1.4- to 24-week time spans. This is comparable to the variation of, for example, low-density lipoprotein cholesterol (8.6% and 19.7%, respectively). Another limitation is that the presence of carotid plaque depends on the definition and that assessment of plaque is user dependent. However, reproducibility in the Malmö Diet and Cancer Study has been shown to be good, and the assessment of carotid plaque was performed by experienced and certified sonographers. Carotid plaque was only measured for the right carotid artery, which is another limitation. Yet, plaque prevalence is comparable with previous studies, measuring both carotid arteries. In addition, we had insufficient information about ischemic stroke subtypes, which would be desirable in future studies.

In conclusion, orosomucoid is associated with increased risk of stroke. Subjects with carotid plaque have higher levels of orosomucoid, and the joint effect substantially increases the risk of stroke, independently of hsCRP levels.

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Disclosures

None.

References


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