Calf Circumference Is Inversely Associated With Carotid Plaques

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Background and Purpose—The association of carotid atherosclerosis with body composition and fat distribution is poorly understood. We aimed to test the cross-sectional association of carotid plaques and common carotid artery intima-media thickness with calf circumference (CC), representing peripheral fat and lean mass, and with waist circumference and waist-to-hip ratio, 2 markers of abdominal obesity.

Methods—The study was performed on 6265 subjects aged ≥65 years recruited prospectively from the electoral rolls of 3 French cities. Ultrasound examination and anthropometric measures were performed according to a standardized protocol.

Results—Carotid plaques were less frequent with increasing CC, the ORs for the second, third, and fourth quartile of CC compared with the first quartile being 0.98 (95% CI, 0.84 to 1.15), 0.85 (95% CI, 0.72 to 1.01), and 0.71 (95% CI, 0.58 to 0.86; P for trend = 0.0002), respectively, independently of age, gender, body mass index, and other vascular risk factors. There was an opposite and multiplicative effect of CC and waist-to-hip ratio on the frequency of carotid plaques (55.1% of individuals in the fourth waist-to-hip ratio quartile and the first CC quartile had carotid plaques, against 31.8% in the first waist-to-hip ratio and the fourth CC quartile). Mean common carotid artery intima-media thickness was larger with increasing waist circumference, waist-to-hip ratio, and CC, but the association with CC disappeared after adjusting for body mass index.

Conclusion—The present study shows, for the first time, an inverse relationship between carotid plaques and CC. Although this needs to be confirmed in other populations, it may suggest an antiatherogenic effect of large CC.

Key Words: atherosclerosis ■ carotid artery ■ carotid intimal medial thickness ■ epidemiology ■ ultrasound

There is growing evidence that body composition and fat distribution are of major importance in determining vascular risk, whereas global body mass may not be such a good predictor of atherosclerosis and vascular events.1,2 Coronary heart disease and vascular events such as stroke, myocardial infarction, and cardiac death appear to be strongly associated with abdominal obesity and upper versus lower fat localization.3–5 More recently, peripheral adiposity was found to be negatively associated with markers of atherosclerosis such as aortic calcifications,6 coronary angiography score,7 and arterial stiffness,8 and it has been suggested that peripheral fat mass may exhibit antiatherogenic effects.

Carotid plaques and elevated carotid intima-media thickness (IMT) are powerful and independent predictors of ischemic stroke, coronary events, and vascular mortality,9–12 that can easily and noninvasively be assessed in large population samples and can be an interesting tool for the follow-up of prevention strategies. The association of these carotid parameters with markers of body composition and fat distribution has not been fully explored yet. Indeed, several studies have demonstrated an association between carotid IMT and anthropometric markers of abdominal obesity (waist circumference, waist-to-hip ratio, sagittal/transverse ratio),13–21 but very little data are available on the association of those markers with carotid plaques,21 a more advanced marker of carotid atherosclerosis than IMT. It is also poorly understood whether markers of body composition other than abdominal obesity such as calf circumference22 are associated with carotid atherosclerosis.

The aim of the present study was to explore more in detail the association of carotid atherosclerosis with several anthropometric markers of body composition in a large population-
based sample of elderly subjects. Our 2 major interests were (1) to assess the relationship of carotid plaques with 2 common markers of abdominal obesity, waist circumference (WC) and waist-to-hip ratio (WHR),23–25 because published data on this subject are insufficient; and (2) to test whether calf circumference (CC), a rarely used anthropometric marker representing lean mass and peripheral fat, is associated with carotid plaques or IMT, which has never been evaluated before.

Materials and Methods

Study Population and Design

This study was performed within the Three-City (3C) Study, a 3-center prospective cohort study whose design has been described in detail elsewhere.26 To be eligible for the study, persons had to be (1) living in the French cities of Bordeaux, Dijon, Montpellier, or their suburbs and registered on the electoral rolls; (2) aged 65 years or over; and (3) noninstitutionalized. Twenty-four percent of the eligible persons selected on the electoral rolls (n=34 922) could not be reached; among those contacted, the acceptance rate was 37%, which is in the same range as the acceptance rate of other population-based prospective cohort studies in the elderly.27 A total of 9693 persons were included between March 1999 and March 2001. Three hundred ninety-nine persons were subsequently excluded, 7 because they were aged <65 years and 392 because they refused to participate in the interview. A baseline ultrasound examination of the carotid arteries was proposed to participants younger than age 85 who were able to come to the examination centers. Due to logistic concerns, the ultrasound examination was not offered to persons included during the last 4 months of subject recruitment. Overall, 73.7% of the participants younger than 85 years (n=6631) had carotid ultrasound measures. As expected, compared with subjects who did not undergo ultrasound examinations, subjects who were able to come to the examination centers to undergo ultrasound examinations had lower means of age (73.5±5.4 years versus 74.5±5.1 years; P<0.001), body mass index (25.6±4.2 kg/m² versus 25.9±4.0 kg/m²; P=0.01), systolic blood pressure (145.2±21.1 versus 151.0±23.9 mm Hg; P<0.001), and total cholesterol (5.7±0.97 versus 5.96±1.03 mmol/L; P<0.01). Due to a few missing data for the variables of interest, the present study was performed in 6265 subjects.

Ultrasound Examination

For the ultrasound examination, the B-mode system (Ultramark 9 High Definition Imaging) with a 5- to 10-MHz sounding was used at each of the 3 centers, and a centralized reading was performed according to a standardized protocol. The procedure has been described in detail elsewhere.28 The examination involved scanning of the common carotid arteries, the carotid bifurcations, and the origin of the internal carotid arteries. The near and far walls of these arterial segments were scanned longitudinally and transversally to assess, at the time of the examination, the presence of plaques. The presence of plaques was defined as localized echo structures encroaching into the vessel lumen for which the distance between the lumen–intima interfaces along at least 0.5 cm of length was ≥1 mm on the common carotid arteries, the carotid bifurcations, and the internal carotid arteries. For IMT measurement, far and near walls of the right and the left common carotid arteries (CCAs) 2 to 3 cm proximal to the bifurcation were imaged. For each side, at least one optimal longitudinal image was frozen in end-diastole by electrocardiographic R-triggering. All frozen images were transferred to a computer system (LØTEC) and digitized into 640×580 pixel cells with 256 gray levels.29 They were stored on CD-ROMs that were sent to the reference center weekly. The IMT was measured at a site free of any discrete plaques along a 10-mm long segment of the far wall of the CCA as the distance between the lumen–intima interface and the media–adventitia interface. On average, 75 measurements were automatically performed on each image and on each side and a mean CCA-IMT value was computed for each side. The CCA-IMT value used in the analyses was a mean of right and left mean values. Lumen diameter was defined as the average of the distances between the 2 leading edges of far wall and near wall lumen–intima interfaces along at least 0.5 cm of length using a computerized validated program as described previously.28

All ultrasounds were read at a Reference Reading Center (Hôpital Broussais, Paris, France) by one trained reader. To ensure reliability and validity of these measurements, programs of centralized training and regular quality control were implemented for the sonographers (n=7) and the reader. Besides, a reproducibility study was performed.30 One hundred fourteen subjects underwent 2 ultrasound examinations performed blindly by 2 different sonographers during the same visit. The mean absolute difference and correlation coefficient between repeated examinations of CCA-IMT were, respectively, 0.06 mm and 0.71. For carotid plaques, the kappa coefficient for agreement between the 2 examinations was 0.78.

Medical History and Standard Biological Parameters

Information about demographic background, medical history, and personal habits was collected during a face-to-face interview using a standardized questionnaire administered by trained nurses.

Personal history of vascular disease was defined as a history of stroke, myocardial infarction, angina pectoris, coronary surgery, or angioplasty. Physical activity was defined as a 3-class variable: light physical activity for subjects practicing no sport (hiking, aerobics, swimming) and walking less than 1 hour per day, mild physical activity for subjects practicing sport regularly but less than once a week or for subjects practicing no sport and walking at least 2 hours per day, and moderate to high physical activity for subjects practicing sport at least once a week or subjects practicing some sport but less than once a week and walking at least 2 hours per day. Information on physical activity was available for 2 of the 3 centers only in 4612 subjects. Baseline blood pressure was measured twice in a sitting position using a digital tensiometer (OMRON M4).

Centralized measurements of biological parameters were performed. Fasting total cholesterol, high-density lipoprotein (HDL) cholesterol, triglyceride, and glucose levels were measured at baseline. Low-density lipoprotein cholesterol was calculated according to the Friedewald formula (low-density lipoprotein=total cholesterol−HDL−[triglycerides/2.2]) and was considered as missing for triglyceride values >4.5 mmol/L. For the statistical analyses, a log transformation of the triglyceride levels was performed. Hypertension was defined as a systolic blood pressure ≥160 mm Hg and/or a diastolic blood pressure ≥95 mm Hg and/or a blood pressure-lowering therapy, hypercholesterolemia as total cholesterol ≥6.20 mmol/L and/or a cholesterol-lowering therapy, and diabetes mellitus as a fasting glucose ≥7 mmol/L and/or an antidiabetic therapy.

Baseline body mass index (BMI) was calculated as the ratio of weight (kg) to the square of height (m²). Anthropometric measures were performed at baseline using a nonelastic but flexible plastic tape. Calf circumference was measured on the left leg (or the right leg for left-handed persons) in a sitting position with the knee and ankle at a right angle and feet resting on the floor. The CC was measured at the point of greatest circumference. Waist circumference was measured midway between the last rib and the top of the iliac crest. Hip circumference was measured at the level of the trochanter major. Waist-to-hip ratio was calculated as the ratio of waist-to-hip circumferences.

The metabolic syndrome was defined according to the National Cholesterol Education Panel III criteria,30 which require the presence of 3 or more alterations among the following: large waist circumference (>88 cm in women and >102 cm in men), elevated triglycerides (≥150 mg/dL), low HDL cholesterol (men <40 and women <50 mg/dL), elevated fasting glucose (≥110 mg/dL), and elevated systolic (≥130 mm Hg) or diastolic blood pressure (≥85 mm Hg) or use of antihypertensive medications.
The unadjusted associations of population characteristics with gender-specific quartiles of CC are presented in Table 1. Increasing CC was significantly associated with hypertension and metabolic syndrome, with increasing triglycerides, and with decreasing age and HDL cholesterol. History of vascular disease was significantly less frequent with increasing CC.

In a univariate analysis, increasing WHR and WC were both significantly associated with hypertension, diabetes, and metabolic syndrome with increasing age, BMI, tobacco consumption, alcohol consumption, triglycerides and total cholesterol, and with decreasing HDL cholesterol. History of vascular disease was significantly more frequent with increasing WHR and WC (data not shown).

Increasing age, male gender, vascular risk factors, and history of vascular disease were significantly associated with both increasing frequency of carotid plaques and increasing

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### Table 1. Population Characteristics According to Gender-Specific Quartiles of CC

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<tr>
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<th>CC</th>
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<td></td>
<td>Quartile 1*</td>
<td>Quartile 2</td>
<td>Quartile 3</td>
<td>Quartile 4</td>
<td>For Trend</td>
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<tr>
<td>n</td>
<td>1560</td>
<td>1641</td>
<td>1576</td>
<td>1488</td>
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<tr>
<td>Women, %</td>
<td>59.6</td>
<td>58.7</td>
<td>59.6</td>
<td>64.6</td>
<td>0.005</td>
<td></td>
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<tr>
<td>Age, years</td>
<td>74.3 ± 5.1</td>
<td>73.6 ± 4.8</td>
<td>73.3 ± 4.9</td>
<td>72.8 ± 4.7</td>
<td>&lt; 0.0001</td>
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<tr>
<td>Hypertension, %</td>
<td>72.2</td>
<td>74.1</td>
<td>75.3</td>
<td>79.9</td>
<td>&lt; 0.0001</td>
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<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>143.4 ± 21.6</td>
<td>144.9 ± 21.1</td>
<td>146.0 ± 21.7</td>
<td>146.1 ± 20.2</td>
<td>&lt; 0.0001</td>
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<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>80.0 ± 11.0</td>
<td>81.7 ± 10.8</td>
<td>82.6 ± 11.1</td>
<td>83.8 ± 10.9</td>
<td>&lt; 0.0001</td>
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<tr>
<td>Antihypertensive treatment, %</td>
<td>43.0</td>
<td>45.0</td>
<td>45.9</td>
<td>54.5</td>
<td>&lt; 0.0001</td>
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<tr>
<td>Alcohol consumption, g/day</td>
<td>13.0 ± 14.3</td>
<td>13.7 ± 14.8</td>
<td>14.1 ± 16.0</td>
<td>11.9 ± 15.0</td>
<td>0.10</td>
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<tr>
<td>Smoking habits, %</td>
<td>61.5</td>
<td>61.1</td>
<td>60.3</td>
<td>62.0</td>
<td>0.33</td>
<td></td>
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<tr>
<td>Never</td>
<td>31.7</td>
<td>33.1</td>
<td>34.5</td>
<td>32.9</td>
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<td></td>
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<tr>
<td>Former smoker</td>
<td>6.8</td>
<td>5.8</td>
<td>5.2</td>
<td>5.1</td>
<td></td>
<td></td>
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<tr>
<td>Current smoker</td>
<td>57.2</td>
<td>56.6</td>
<td>55.7</td>
<td>53.9</td>
<td>0.06</td>
<td></td>
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<tr>
<td>Hypercholesterolemia, %</td>
<td>5.82 ± 0.98</td>
<td>5.78 ± 0.96</td>
<td>5.78 ± 0.95</td>
<td>5.71 ± 0.96</td>
<td>0.004</td>
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<tr>
<td>Total cholesterol, mmol/L</td>
<td>1.68 ± 0.42</td>
<td>1.64 ± 0.42</td>
<td>1.59 ± 0.40</td>
<td>1.54 ± 0.37</td>
<td>&lt; 0.0001</td>
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<tr>
<td>Low-density lipoprotein cholesterol, mmol/L</td>
<td>3.60 ± 0.84</td>
<td>3.60 ± 0.85</td>
<td>3.61 ± 0.83</td>
<td>3.56 ± 0.83</td>
<td>0.26</td>
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<tr>
<td>Triglycerides, mmol/L</td>
<td>1.19 ± 0.57</td>
<td>1.22 ± 0.61</td>
<td>1.27 ± 0.64</td>
<td>1.36 ± 0.64</td>
<td>&lt; 0.0001</td>
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<tr>
<td>Lipid-lowering drugs intake, %</td>
<td>30.4</td>
<td>30.7</td>
<td>30.8</td>
<td>32.1</td>
<td>0.34</td>
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<tr>
<td>Diabetes, %</td>
<td>9.6</td>
<td>8.1</td>
<td>9.7</td>
<td>11.0</td>
<td>0.08</td>
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<tr>
<td>Metabolic syndrome, %</td>
<td>7.7</td>
<td>11.6</td>
<td>15.3</td>
<td>27.5</td>
<td>&lt; 0.0001</td>
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<tr>
<td>History of vascular disease, %</td>
<td>3.0</td>
<td>2.9</td>
<td>2.7</td>
<td>3.0</td>
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<tr>
<td>Physical activity, †</td>
<td>44.9</td>
<td>42.6</td>
<td>39.5</td>
<td>47.9</td>
<td>0.55</td>
<td></td>
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<tr>
<td>Light</td>
<td>36.9</td>
<td>36.5</td>
<td>37.8</td>
<td>35.0</td>
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<tr>
<td>Mild</td>
<td>18.2</td>
<td>20.9</td>
<td>22.7</td>
<td>17.1</td>
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<tr>
<td>BMI, kg/m²</td>
<td>22.6 ± 2.9</td>
<td>24.6 ± 2.7</td>
<td>26.2 ± 3.0</td>
<td>29.3 ± 3.9</td>
<td>&lt; 0.0001</td>
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<tr>
<td>WHR</td>
<td>0.87 ± 0.09</td>
<td>0.88 ± 0.09</td>
<td>0.88 ± 0.09</td>
<td>0.89 ± 0.08</td>
<td>&lt; 0.0001</td>
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<tr>
<td>WC</td>
<td>82.0 ± 0.29</td>
<td>86.8 ± 0.28</td>
<td>89.7 ± 0.29</td>
<td>96.1 ± 0.29</td>
<td>&lt; 0.0001</td>
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</table>

Data are mean ± SD or % as indicated.
*Lowest quartile.
†Based on log-transformed values.
‡Information on physical activity was available in 4612 subjects.
Calf circumference was associated with carotid plaques (frequency of carotid plaques = 49.5%, 43.1%, and 37.6% in individuals performing light, mild, and moderate to high physical activity, respectively; P < 0.0001). Increasing BMI was significantly associated with increasing CCA-IMT and increasing frequency of carotid plaques, but for carotid plaques, the association disappeared after adjustment for age, gender, vascular risk factors, and history of vascular disease (Supplemental Table I, available online at http://stroke.ahajournals.org). The correlation coefficients among the 3 anthropometric measures under study were 0.75 (P < 0.0001) between WHR and WC, 0.27 (P < 0.0001) between WHR and CC, and 0.54 (P < 0.0001) between WC and CC. BMI was correlated with WHR (r = 0.35, P < 0.0001), WC (r = 0.77, P < 0.0001), and CC (r = 0.64, P < 0.0001).

**Association of Calf Circumference With Carotid Plaques, Common Carotid Artery Intima-Media Thickness, and Carotid Diameter**

Carotid plaques were significantly less frequent with increasing CC, even after adjusting for age, gender, vascular risk factors, and history of vascular disease. Additionally adjusting for BMI did not modify the results and even strengthened the association (Table 2). When adding physical activity to the latter model, results were also unchanged, the ORs for the second, third, and fourth quartiles of CC compared with the first quartile being 0.97 (95% CI, 0.81 to 1.16), 0.74 (95% CI, 0.60 to 0.91), and 0.63 (95% CI, 0.50 to 0.80; P for trend < 0.0001). Adjusting for WC instead of BMI yielded similar results (data not shown). Excluding subjects with overt cardiovascular disease and subjects with a metabolic syndrome did not modify the results (Supplemental Table II). The association of carotid plaques with CC was substantially unchanged after stratifying on gender, BMI, and physical activity, although it was only borderline significant in men (Supplemental Table II), and there was no significant interaction between CC and gender, BMI, or physical activity. We did not find any significant interaction either between CC and WHR or WC. There was, however, an opposite and multiplicative relationship of CC and WHR with carotid plaques as depicted in the Figure. Individuals with the smallest quartile of WHR and the largest quartile of CC had the lowest frequency of carotid plaques (31.8%), whereas those with the largest quartile of WHR and the smallest quartile of CC group had the highest frequency of carotid plaques (55.1%; Figure).

There was also a significant linear relationship between CC quartiles and the number of sites with plaques. The frequency of subjects with a CC in the fourth quartile was 25.3%, 22.4%, and 21.7% among subjects with no plaque, one site with plaques, and 2 or more sites with plaques, respectively, whereas the frequency of subjects with a CC in the first quartile was 23.8%, 25.5%, and 26.5% among subjects with no plaque, one site with plaques, and 2 or more sites with plaques (P for linear association = 0.001).

CCA-IMT was higher with increasing CC, even after adjusting for age, gender, vascular risk factors, and history of vascular disease, but the association disappeared after adjusting additionally for BMI or WC (Table 2). Similarly, CCA diameter was higher with increasing CC, but the relationship...
was largely attenuated after adjusting for BMI (data not shown).

**Association of Waist-to-Hip Ratio and Waist Circumference With Carotid Plaques and Common Carotid Artery Intima-Media Thickness**

WHR and WC quartiles were associated with increasing frequency of carotid plaques, but this association was diminished after adjusting for vascular risk factors (Table 3). The association was stronger again after adjusting for CC quartiles ($P=0.04$ for WC and $P=0.05$ for WHR).

Both WHR and WC quartiles were significantly associated with increasing CCA-IMT, even after adjusting for age, gender, vascular risk factors, and history of vascular disease (Table 3). Additionally, adjusting for CC did not modify these results (data not shown). All these results were substantially unchanged after adjusting additionally for physical activity. The association of WHR or WC with CCA-IMT was the same after stratifying for the presence of carotid plaques (data not shown).

**Discussion**

In this population-based study on 6265 subjects aged $\geq 65$ years, we demonstrated for the first time that carotid plaques were significantly less frequent with increasing CC independently of age, gender, vascular risk factors, BMI, abdominal obesity, and physical activity. There was an opposite and multiplicative relationship of CC and WHR with the frequency of carotid plaques, the highest frequency being found in subjects with the highest quartile of WHR and the lowest quartile of CC. Mean CCA-IMT was larger with increasing WHR, WC, and CC, but in the case of CC, the association disappeared after adjusting for BMI.

Measures of CCA-IMT and carotid plaques have been validated previously and have a high reproducibility.\footnote{Of course, replication of our results in independent populations is required. It should also be noted that our population is not perfectly representative of the French general population aged $\geq 65$ years, because only noninstitutionalized individuals who accepted to take part in a follow-up study and who were able to come to the study examination centers were included. Persons who participate in a follow-up study are likely to be more health-conscious and might have less risk factors and diseases than nonparticipants. This limitation is common to most large population-based prospective studies, whatever the sampling procedure used. There are, however, no French national data that would permit to determine precisely how different the 3C Study participants are and whether they had better medical follow-up and health care than the general elderly population. Among the 3C Study participants, those who were able to come to the examination centers to undergo ultrasound examinations were younger and had lower BMI, systolic blood pressure, and total cholesterol than those who did not undergo ultrasound examinations.}

**Table 3. Association of Carotid Parameters With WC and WHR**

<table>
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<tr>
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<th>WC</th>
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<th>P for Trend</th>
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<tr>
<td>n</td>
<td></td>
<td>Quartile 1*</td>
<td>Quartile 2</td>
<td>Quartile 3</td>
<td>Quartile 4</td>
</tr>
<tr>
<td>Carotid plaques, %</td>
<td></td>
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<tr>
<td>No adjustment, %</td>
<td>41.5</td>
<td>44.9</td>
<td>50.2</td>
<td>51.2</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>Multivariable OR (95% CI)$^\dagger$</td>
<td>1</td>
<td>1.03 (0.88–1.20)</td>
<td>1.13 (0.97–1.32)</td>
<td>1.01 (0.85–1.19)</td>
<td>0.64</td>
</tr>
<tr>
<td>CCA-IMT, mm, mean±SE</td>
<td></td>
<td></td>
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<tr>
<td>No adjustment, mm</td>
<td>0.690±0.003</td>
<td>0.709±0.003</td>
<td>0.719±0.003</td>
<td>0.734±0.003</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>Multivariable,$^\dagger$ mm</td>
<td>0.695±0.003</td>
<td>0.712±0.003</td>
<td>0.717±0.003</td>
<td>0.729±0.003</td>
<td>$&lt;0.0001$</td>
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<table>
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<th>WHR</th>
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<td></td>
<td>Quartile 1*</td>
<td>Quartile 2</td>
<td>Quartile 3</td>
<td>Quartile 4</td>
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<tr>
<td>Carotid plaques, %</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>No adjustment, %</td>
<td>39.8</td>
<td>46.5</td>
<td>48.9</td>
<td>52.6</td>
<td>$&lt;0.0001$</td>
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<tr>
<td>Multivariable OR (95% CI)$^\dagger$</td>
<td>1</td>
<td>1.16 (1.00–1.36)</td>
<td>1.15 (0.98–1.35)</td>
<td>1.15 (0.98–1.35)</td>
<td>0.13</td>
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<td>CCA-IMT, mm, mean±SE</td>
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<tr>
<td>No adjustment, mm</td>
<td>0.695±0.003</td>
<td>0.704±0.003</td>
<td>0.719±0.003</td>
<td>0.733±0.003</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>Multivariable,$^\dagger$ mm</td>
<td>0.703±0.003</td>
<td>0.707±0.003</td>
<td>0.716±0.003</td>
<td>0.727±0.003</td>
<td>$&lt;0.0001$</td>
</tr>
</tbody>
</table>

*Lowest quartile.

$^\dagger$Adjusted for age, gender, smoking habits, alcohol consumption, systolic blood pressure, antihypertensive treatment, HDL cholesterol, low-density lipoprotein cholesterol, triglycerides (log-transformed value), lipid-lowering drugs, diabetes, history of vascular disease.
the inverse association between carotid plaques and CC was graded; (3) that it was independent of age, gender, vascular risk factors, BMI, and physical activity; and (4) that stratifying on gender, BMI, and physical activity or excluding subjects with a metabolic syndrome or a history of vascular event did not modify the results. The graded inverse association of CC with prevalent vascular events is also in line with our main finding.

The fact that CC was associated with carotid plaques and not with CCA-IMT in a multivariable model may suggest that CC could be involved in later stages of atherosclerosis. Furthermore, elevated CCA-IMT may in some instances reflect a nonatherosclerotic thickening, and the ultrasound technique is unable to differentiate an atherosclerotic from a nonatherosclerotic cause of arterial wall thickening. As a matter of fact, because the association between CCA-IMT and CC disappeared after adjusting for BMI, it may just reflect an arterial wall thickening in response to increased global body mass. Increased body mass requires increased blood supply, which implies size adaptation of the arteri-ies, and in response to increased arterial diameter, thick-ening of the arterial wall may occur to maintain normal wall stress. Accordingly, animal studies have shown that the overall wall thickness, mainly reflecting the number of smooth muscle cell layers, reflects the size of the animal and the diameter of the vessel. Indeed, in the present study, we found that increasing CC quartiles was also associated with increasing CCA diameter and this relationship was attenuated after adjusting for BMI. A limitation here is that, using ultrasound, it is not possible to distinguish between intima and media thickening. Therefore, we were unable to determine whether increased IMT in our population reflected intimal atherosclerosis or medial adaptive response to hemo-dynamic alterations.

Calf circumference is a surrogate marker of lean mass and peripheral subcutaneous fat, the relative importance of each component depending on the nutritional status, and the global body mass. If the inverse association we observed between CC and carotid plaques is true, and if it is causal, there are several potential underlying mechanisms. One explanation could be a protective effect of peripheral subcutaneous fat on the occurrence of atherosclerosis. Indeed, recent studies found peripheral adiposity to be negatively associated with type 2 diabetes and with several markers of atherosclerosis such as aortic calcifications, coronary angiography score, and arterial stiffness. Peripheral subcutaneous fat, compared with abdominal and in particular visceral fat, has a low rate of lipolysis and is therefore more likely to take up free fatty acids from the circulation and less likely to release them. Increased peripheral fat stores may protect the liver and other organs from high free fatty acid exposure and thus from insulin resistance. Furthermore, differences in gene expression between visceral and subcutaneous adipocytes may also play a role with a more proatherogenic pattern of gene expression in visceral fat. Alternatively, the inverse relationship between carotid plaques and increasing CC may also reflect a protective effect of large amounts of lean mass from calf muscles. Two studies have assessed the relationship between body composition (using dual-energy x-ray absorptiometry) and IMT showing a nonsignificant trend of increasing IMT with increasing peripheral lean mass and no association with peripheral or trunk fat mass in the first study and no association at all in the second study. These studies were, however, performed on smaller samples (336 and 648 participants, respectively) of younger individuals and did not include an evaluation of carotid plaques. Further studies on larger and older populations, implementing imaging devices such as dual-energy x-ray absorptiometry or CT and MRI to measure the muscle and fat component within the calf, could improve our understanding of the respective roles played by calf muscle and fat mass in association with carotid plaques.

Although we cannot rule out a participation of increased physical activity in our results, we believe that it is unlikely to be the only explanation. First, we did not observe a linear increase in physical activity with increasing CC quartiles (Table 1), and although CC was found to be well correlated with total muscle in the malnourished elderly, this association is less clear in healthier elderly subjects. Second, the association between CC and carotid plaques was unchanged after adjusting for and stratifying on physical activity. It should be mentioned that the variable we used to quantify physical activity has not been formally validated.

Association of Waist-to-Hip Ratio and Waist Circumference With Carotid Plaques and Common Carotid Artery Intima-Media Thickness

Several studies had already shown that CCA-IMT was significantly associated with anthropometric markers of abdominal obesity but failed to show any association of these markers with carotid plaques, although very little data are available on the latter association. In the present study, supporting previous results, we confirmed the positive association of CCA-IMT with WHR and WC. We also found an association of WHR (and WC) with carotid plaques, which became borderline or nonsignificant after adjusting for vascular risk factors and history of vascular disease. Interestingly, the strength of the association increased after adjusting for CC, suggesting a confounding effect of the latter. CC was indeed strongly correlated with WHR and vice versa related with carotid plaques. A positive association of abdominal fat markers with carotid plaques may thus be masked if CC is not adjusted for. The multiplicative and opposite effect of CC and WHR on the frequency of carotid plaques suggests that both measures should be taken into account jointly when assessing vascular risk profiles.

To conclude, in a large population-based study on subjects aged ≥65 years, we found that carotid plaques were significantly less frequent in subjects with a large CC independently of vascular risk factors, global body mass, and physical activity. There was an opposite and multiplicative effect of WHR and CC, subjects with the smallest quartile of CC and the largest quartile of WHR showing the highest frequency of carotid plaques. Our results suggest that CC may be a new anthropometric marker to take into account when assessing the risk of carotid atherosclerosis. Validation of this finding in independent populations is required. Future studies should also test the association of CC with plaque composition...
(using more detailed measures than ultrasound such as MRI), with plaque progression, and with vascular events. Besides, research focusing on the underlying mechanisms, and in particular the respective role of lean mass and peripheral fat mass, is warranted.

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References


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