A Detailed Cardiovascular Characterization of Obesity Without the Metabolic Syndrome

Lars Lind, Agneta Siegbahn, Erik Ingelsson, Johan Sundström, Johan Ärnlov

Objective—Although obesity without metabolic disturbances has been regarded as harmless, we have recently shown that obese subjects without the metabolic syndrome (MetS) has an increased risk of cardiovascular (CV) disorders and mortality during long-term follow-up. To investigate the basis for that increased risk, we studied the impact of obesity without MetS on multiple markers of subclinical CV disease.

Methods and Results—At age 70, 1016 subjects were investigated in the Prospective Investigation of the Vasculature in Uppsala Seniors study. According to body mass index (BMI)/MetS status, they were categorized as normal weight (BMI <25 kg/m²) without MetS (National Cholesterol Education Program criteria, n = 319), normal weight with MetS (n = 19), overweight (BMI 25 to 29.9 kg/m²) without MetS (n = 333), overweight with MetS (n = 94), obese (BMI ≥30 kg/m²) without MetS (n = 102), and obese with MetS (n = 118). Several different measurements of endothelial reactivity, arterial compliance (plethysmography and ultrasound), carotid artery atherosclerosis, and echocardiography were performed, and 7 markers of coagulation/fibrinolysis were measured. Subjects with obesity without MetS showed impaired reactivity, a more echoluent carotid artery wall, increased left ventricular mass and function together with impaired coagulation/fibrinolysis compared with normal-weight subjects without the MetS (P<0.05 to 0.001). The majority of these disturbances were also seen in overweight subjects without the MetS.

Conclusion—In contrast to some previous studies, our data do not support that obesity without MetS is a benign condition, because obesity without MetS was associated with impairments in multiple markers of subclinical CV disease. This was also the case for overweight subjects without the MetS. (Arterioscler Thromb Vasc Biol. 2011;31:e27-e34.)

Key Words: epidemiology ■ metabolism ■ obesity ■ risk factors ■ metabolic syndrome

Obesity is a growing problem in the industrialized world, and it is now frequently also seen in developing countries. Obesity is not only associated with major cardiovascular (CV) risk factors, such as hypertension, dyslipidemia, and diabetes, but is also a risk factor related to future CV events. Furthermore, obesity, especially of the abdominal type, is one of the cornerstones of the metabolic syndrome (MetS), a condition that might add predictive power to the classical CV risk factors.

It has, however, been highlighted that not every obese subject has a deranged metabolic profile, and the term metabolically healthy obese (MHO) has been coined. When MHO has been defined according to the degree of insulin sensitivity, MHO has been associated with less dyslipidemia, less inflammation, and less visceral fat than obese subjects with insulin resistance (IR). In a few previous studies, it has also been suggested that the MHO do not show an increased risk for CV disease or mortality compared with nonobese subjects without the MetS.

Conversely, Kuk and Ardern showed that MHO was associated with an increased mortality risk. Moreover, when we followed a cohort of middle-aged men for a prolonged follow-up period (28 years), subjects with obesity without MetS showed an almost doubled risk for both total mortality and major CV events compared with normal-weight subjects without the MetS. Also of interest was the finding that not only was an increased risk seen in obesity without MetS but also that overweight subjects without the MetS showed an increased risk for both total mortality and major CV events. The conflicting results from previous longitudinal studies investigating the association with future CV events and death may be due to differences in the definition of MHO, the outcomes, length of follow-up, and differences in gender, age, and ethnicity of the study samples.

Based on our previous data of an increased CV risk in obesity without MetS, we hypothesized that obesity without MetS was associated with impairments in markers of subclinical CV disease compared with normal-weight subjects without the MetS. Therefore, we investigated this primary hypothesis using the community-based Prospective Investigation of...
the Vasculature in Uppsala Seniors study, in which we have measured indices of CV structure and function by several different techniques regarding vascular function, atherosclerosis, and left ventricular geometry and function and markers of coagulation/fibrinolysis in an elderly cohort. As secondary aims, we also investigated the impact of overweight on these markers of subclinical CV disease. Furthermore, in line with our previous study, we also investigated markers of subclinical CV disease in combinations of body mass index (BMI) and IR (according to the homeostasis model assessment [HOMA] index) instead of using combinations of BMI and the MetS.

Materials

Subjects

Eligible were all subjects aged 70 living in the community of Uppsala, Sweden. The subjects were chosen from the register of community living and were invited in a randomized order from the start of the study in April 2001 to the last included subject in June 2004. The subjects received an invitation by letter within 1 month of their 70th birthday to standardize for age. Of the 2025 subjects invited, 1016 subjects were investigated, giving a participation rate of 50.1%.

The study was approved by the ethics committee of the University of Uppsala, and the participants gave informed consent.

Baseline Investigation

The participants were asked to answer a questionnaire about their medical history, smoking and exercise habits, and regular medication.

All subjects were investigated in the morning after an overnight fast. No medication or smoking was allowed after midnight. After recordings of height, weight, and abdominal and hip circumferences, fasting was required. No medication or smoking was allowed after midnight. After 30 minutes of rest, and the average of 3 recordings was used. Lipid variables and fasting blood glucose were measured by standard laboratory techniques.

Approximately 10% of the cohort reported a history of coronary heart disease, 4% reported stroke, and 9% reported diabetes mellitus. Almost half the cohort reported any CV medication (45%), with antihypertensive medication being the most prevalent (32%). Fifteen percent reported use of statins, whereas insulin and oral antiglycemic antihypertensive medication being the most prevalent (32%). Fifteen percent reported use of statins, whereas insulin and oral antiglycemic drugs were reported in 2% and 6%, respectively (see Lind et al18 for details).

MetS was defined by the National Cholesterol Education Program/American Heart Association/Adult Treatment Panel III criteria. Three of the following 5 criteria should be fulfilled: blood pressure ≥130/85 mm Hg or antihypertensive treatment, fasting plasma glucose ≥6.1 mmol/L, serum triglycerides ≥1.7 mmol/L, waist circumference ≥102 cm in men and ≥88 cm in women, high-density lipoprotein (HDL) cholesterol <1.0 mmol/L in men and <1.3 in women.

By defining normal weight as BMI 25 to 29.9 kg/m², overweight as BMI ≥30 kg/m², we could categorize the participants as normal weight without MetS (n = 319), normal weight with MetS (n = 19), overweight without MetS (n = 333), overweight with MetS (n = 94), obese without MetS (n = 102), and obese with MetS (n = 118). A classification in these groups could be performed in only 985 subjects because of some missing data in 31 subjects. Data on CV risk factors in these different groups are given in Table 1.

Serum insulin was measured by an enzymatic-immunologic assay (Roche, Mannheim, Germany). We used the homeostasis model ([Fasting glucose × Fasting insulin]/22.5) to define IR as a HOMA IR index level in the top quartile of the distribution in participants without diabetes in this sample ≥2.6 (mmol/L) × (mU/L)]. By using IR by this definition, we created 6 groups from the combinations of BMI and IR in a similar manner as for BMI and the MetS as described above.

Methods

Carotid Artery Ultrasound Evaluation

The carotid artery was assessed by external B-mode ultrasound imaging (XP128 with a 10-MHz linear transducer, Acuson, Mountain View, CA).

The intima-media thickness (IMT) was measured in the far wall in the common carotid artery (CCA) 1 to 2 cm proximal to the bulb. The images were digitized and imported into the automated Artery Measurement Software for dedicated analysis of IMT and plaque size. A maximal 10-mm segment with good image quality was chosen for IMT analysis from the CCA.

A region of interest was placed manually around the intima-media segment that was evaluated for IMT and the program calculates the intima-media echogenicity (IM-GSM) from analysis of the individual pixels within the region of interest on a scale from 0 (black) to 256 (white). The blood was used as the reference for black, and the adventitia was the reference for white.

The mean length of the evaluated intima-media segments was 9.0 (SD 2.1) mm when subjects with a segment recording less than 5 mm were excluded, leaving 946 subjects with valid recordings.

The measurements of IMT were repeated in 30 random subjects, giving a coefficient of variation of 7.2% for carotid artery IMT and 7.5% for IM-GSM.

For a more detailed description, see Lind et al. The distensibility of the CCA was calculated as the percentage change in diameter maximum to minimum 1 to 2 cm proximal to the bulb in relation to the minimal diameter in diastole divided by the central pulse pressure obtained by pulse wave analysis (Sphygmocor, Pulse Wave Medical Ltd). The stroke volume to pulse pressure ratio used the stroke volume obtained by echocardiography divided by central pulse pressure. For a more detailed description, see Lind et al.20

The Invasive Forearm Technique

Forearm blood flow (FFB) was measured by venous occlusion plethysmography (Elektromedicin, Kullavik, Sweden) with the strain-gauge technique. An arterial cannula was placed in the brachial artery. Resting FBF was measured 30 minutes after cannula insertion, and local intraarterial drug-infusions were given for 5 minutes for each dose with a 20-minute washout period between the drugs. The infused dosages were 25 and 50 µg/minute for acetylsalicylic acid (Clim-alpha, Switzerland) and 5 and 10 µg/minute for sodium nitroprusside (Nitropress, Abbot). The drugs were given in a random order at a maximal rate of 1 mL/minute.

Endothelium-dependent vasodilatation (EDV) with this technique was defined as FBF during infusion of 50 µg/minute acetylsalicylic acid minus resting FBF divided by resting FBF. Endothelium-independent vasodilatation (EIDV) was defined as FBF during infusion of 10 µg/minute of sodium nitroprusside minus resting FBF divided by resting FBF. The CV for EDV and EIDV were 8% to 10%. For a more detailed description, see Lind et al.

The Brachial Artery Ultrasound Technique

The brachial artery was assessed by external B-mode ultrasound imaging 2 to 3 cm above the elbow (Acuson XP128 with a 10-MHz linear transducer). A cuff was placed below the elbow and inflated to a pressure at least 50 mm Hg above systolic blood pressure for 5 minutes. Flow-mediated dilatation was defined as the maximal brachial artery diameter recorded between 30 and 90 seconds following cuff release minus diameter at rest divided by the diameter at rest. The CV was 3% for baseline brachial artery diameter and 29% for flow-mediated dilatation. For a more detailed description, see Lind et al.18
Echocardiography and Doppler
A comprehensive 2-dimensional and Doppler echocardiography was performed with an Acuson XP124 cardiac ultrasound unit. Left ventricular (LV) dimensions were measured with M-mode. Ejection fraction (EF) was determined by the method of Teicholtz. Left intraventricular septum thickness (IVST) was determined from the apical transducer position with pulsed Doppler. The peak velocity of atrial filling wave (E-wave) and the peak velocity of early diastolic filling wave (A-wave) were recorded, and the E to A ratio was calculated. LV isovolumic relaxation time (IVRT) was measured as the time between aortic valve closure and the start of atrial filling (A-wave) and the peak velocity of atrial filling wave (A-wave). The myocardial performance index (MPI) was calculated by the following formula: \((\text{A-E time} - \text{Ejection time}) / \text{Ejection time}\).

Coagulation/Fibrinolysis Factors
The plasma concentrations of von Willebrand factor antigen, tissue plasminogen activator (tPA) antigen, prothrombinfragment (F) 1+2, and t-dimer were analyzed by commercial immunoassays (STA-LLAtestVWF:ag, Stago, France; TintElize tPA, Biopool, Sweden; Enzygnost F 1+2, Dade Behring; and TintElize t-dimer, Biopool). FVIIa, FVIIa-rTF, and fibrinogen with STA-Fibrinogen, both from Diagnostica (Stago, France). Plasminogen activator inhibitor-1 (PAI-1) activity was analyzed by Chromolize PAI-1 Immunoassay from Biopool.

Statistics
Nonnormally distributed continuous variables were log-transformed (all coagulation/fibrinolysis variables, EDV, EIDV, E/A ratio, flow-mediated dilatation, CCA distensibility, and the stroke volume to pulse pressure ratio) to achieve a normal distribution. Differences between groups were evaluated by factorial ANOVA, with post hoc analysis for comparison versus the normal-weight group. All comparisons between the groups in Tables 2 to 4 and the Supplemental Tables (available online at http://atvb.ahajournals.org) were adjusted for gender. A similar secondary analysis was performed after exclusion of subjects with diabetes, myocardial infarction, stroke, or heart failure. STATA10 (Stata Corp, College Station, TX) was used for the calculations.

Results
Vascular Characteristics
Compared with the normal group without the MetS, the obesity without MetS showed reduced EDV, EIDV, and IM-GSM. A similar pattern was also seen in overweight subjects with or without the MetS and in obese subjects with

Table 1. Cardiovascular Risk Factors in Different BMI/MetS Categories (n=985)

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Normal Weight</th>
<th>Overweight</th>
<th>Obese</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects, n (%)</td>
<td>Normal Weight</td>
<td>Overweight</td>
<td>Obese</td>
</tr>
<tr>
<td>Females, %</td>
<td>53</td>
<td>63</td>
<td>59</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>22.7 (1.6)</td>
<td>23.0 (1.2)</td>
<td>33.0 (2.9)</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>144 (22)</td>
<td>149 (30)</td>
<td>152 (22)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>76 (10)</td>
<td>72 (9)</td>
<td>81 (9)</td>
</tr>
<tr>
<td>Fasting blood glucose, mmol/L</td>
<td>4.9 (0.9)</td>
<td>6.7 (3.6)</td>
<td>4.9 (0.4)</td>
</tr>
<tr>
<td>Serum LDL cholesterol, mmol/L</td>
<td>3.4 (0.8)</td>
<td>3.2 (1.1)</td>
<td>3.4 (0.9)</td>
</tr>
<tr>
<td>Serum HDL cholesterol, mmol/L</td>
<td>1.7 (0.4)</td>
<td>1.2 (0.3)</td>
<td>1.5 (0.3)</td>
</tr>
<tr>
<td>Serum triglycerides, mmol/L</td>
<td>1.0 (0.5)</td>
<td>1.7 (0.6)</td>
<td>1.2 (0.4)</td>
</tr>
<tr>
<td>HOMA insulin sensitivity, mmol/L</td>
<td>1.4 (0.9)</td>
<td>4.6 (8.5)</td>
<td>2.0 (2.9)</td>
</tr>
<tr>
<td>Current smoking, %</td>
<td>16</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Hypertension treatment, %</td>
<td>19</td>
<td>68</td>
<td>87</td>
</tr>
<tr>
<td>Diabetes treatment, %</td>
<td>2</td>
<td>36</td>
<td>22</td>
</tr>
<tr>
<td>Statin treatment, %</td>
<td>9</td>
<td>31</td>
<td>18</td>
</tr>
<tr>
<td>Prevalence of MetS components</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated waist circumference, %</td>
<td>1.2</td>
<td>16</td>
<td>81</td>
</tr>
<tr>
<td>Elevated triglycerides, %</td>
<td>6.0</td>
<td>63</td>
<td>2.9</td>
</tr>
<tr>
<td>Reduced HDL, %</td>
<td>6.9</td>
<td>84</td>
<td>4.9</td>
</tr>
<tr>
<td>Elevated blood pressure, %</td>
<td>74</td>
<td>100</td>
<td>87</td>
</tr>
<tr>
<td>Elevated glucose, %</td>
<td>10</td>
<td>58</td>
<td>1.0</td>
</tr>
<tr>
<td>Mean no. of MetS components</td>
<td>1.0</td>
<td>3.2</td>
<td>1.7</td>
</tr>
</tbody>
</table>

Data are means (standard deviations) except where indicated. Normal weight is defined as BMI <25 kg/m²; overweight, BMI 25 to 30 kg/m²; obese, BMI >30 kg/m². Definition of MetS components: Elevated waist circumference, men >102 cm, women >88 cm; elevated triglycerides, ≥1.7 mmol/L; reduced HDL cholesterol, men <1.03 mmol/L, women <1.29 mmol/L; elevated blood pressure, ≥130/85 mm Hg or use of medication for hypertension; elevated fasting glucose, ≥5.6 mmol/L or use of medication for hyperglycemia. LDL indicates low-density lipoprotein.
the MetS. In overweight subjects without the MetS and in obese subjects with the MetS, also, an increase in IMT was found. The 2 indices of arterial compliance did not differ significantly between the groups (see Table 2 for details). All comparisons between the groups were adjusted for gender.

LV Characteristics

Compared with the normal group without the MetS, the obesity without MetS showed increased LVMI, RWT, IVRT, and MPI, together with a reduced EF and E/A ratio. A similar pattern was seen in the obese with the MetS. In the overweight groups, deviations were also seen in LVMI, E/A ratio, and IVRT compared with the normal group without the MetS (see Table 3 for details). All comparisons between the groups were adjusted for gender.

Coagulation and Fibrinolysis

Compared with the normal group without the MetS, the obesity without MetS showed increased levels of tPA antigen, von Willebrand factor, fibrinogen, and PAI-1 activity. A similar pattern was seen in the obese with the MetS. In the overweight groups, deviations were also seen in tPA antigen, fibrinogen, and PAI-1 activity compared with the normal group without the MetS. d-dimer, F 1+2, and FVIIa did not differ significantly between the groups (see Table 4 for details). All comparisons between the groups were adjusted for gender.

Use of IR Instead of the MetS

When defining IR as the upper quartile of HOMA IR index and creating 6 groups according to a combination of BMI and IR in a similar manner as the 6 BMI/MetS groups, no major differences in the number of subjects found in each BMI/IR group was seen compared with the BMI/MetS classification except that the normal-weight group with IR was larger than the normal-weight group with the MetS (see Supplemental Table I).

Regarding the primary hypothesis, obese subjects without IR showed similar significant derangements in the CV and coagulation/fibrinolysis indices compared with normal-weight individuals without IR as when obesity without MetS was compared with normal weight without the MetS above.

Table 2. Vascular Characteristics in Different BMI/MetS Categories

<table>
<thead>
<tr>
<th></th>
<th>Normal Weight</th>
<th></th>
<th>Overweight</th>
<th></th>
<th>Obese</th>
<th></th>
<th>P Value (ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Without MetS</td>
<td>With MetS</td>
<td>Without MetS</td>
<td>With MetS</td>
<td>Without MetS</td>
<td>With MetS</td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>319</td>
<td>19</td>
<td>333</td>
<td>94</td>
<td>102</td>
<td>118</td>
<td></td>
</tr>
<tr>
<td>EDV, %</td>
<td>609 (340)</td>
<td>734 (326)</td>
<td>490 (251)*</td>
<td>452 (318)*</td>
<td>466 (229)*</td>
<td>467 (387)*</td>
<td>0.0001</td>
</tr>
<tr>
<td>EIDV, %</td>
<td>424 (239)</td>
<td>412 (191)</td>
<td>364 (195)†</td>
<td>318 (205)*</td>
<td>312 (148)*</td>
<td>314 (206)*</td>
<td>0.0001</td>
</tr>
<tr>
<td>FMD, %</td>
<td>4.7 (3.6)</td>
<td>4.5 (2.7)</td>
<td>5.0 (3.4)</td>
<td>4.8 (3.7)</td>
<td>4.9 (4.2)</td>
<td>4.0 (3.6)</td>
<td>0.26</td>
</tr>
<tr>
<td>IMT, mm</td>
<td>0.86 (0.14)</td>
<td>0.89 (0.22)</td>
<td>0.89 (0.17)‡</td>
<td>0.90 (0.16)†</td>
<td>0.88 (0.13)</td>
<td>0.94 (0.13)*</td>
<td>0.0023</td>
</tr>
<tr>
<td>IM-GSM, units</td>
<td>83 (24)</td>
<td>83 (26)</td>
<td>77 (22)†</td>
<td>72 (25)*</td>
<td>77 (23)‡</td>
<td>74 (19)*</td>
<td>0.0001</td>
</tr>
<tr>
<td>CCA distensibility, %/mm Hg</td>
<td>98 (51)</td>
<td>87 (40)</td>
<td>92 (44)</td>
<td>88 (42)</td>
<td>92 (41)</td>
<td>83 (46)</td>
<td>0.13</td>
</tr>
<tr>
<td>SV/PP ratio, ml/mm Hg</td>
<td>1.3 (0.5)</td>
<td>1.2 (0.3)</td>
<td>1.4 (0.5)</td>
<td>1.3 (0.5)</td>
<td>1.3 (0.5)</td>
<td>1.3 (0.5)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Data are means (standard deviations). Normal weight is defined as BMI <25 kg/m²; overweight, BMI 25 to 30 kg/m²; obese, BMI >30 kg/m². All comparisons between the groups were adjusted for gender.

*P<0.0001 vs normal weight without the MetS.
†P<0.001 vs normal weight without the MetS.
‡P<0.05 vs normal weight without the MetS.

Table 3. Left Ventricular Characteristics in Different BMI/MetS Categories

<table>
<thead>
<tr>
<th></th>
<th>Normal Weight</th>
<th></th>
<th>Overweight</th>
<th></th>
<th>Obese</th>
<th></th>
<th>P Value (ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Without MetS</td>
<td>With MetS</td>
<td>Without MetS</td>
<td>With MetS</td>
<td>Without MetS</td>
<td>With MetS</td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>319</td>
<td>19</td>
<td>333</td>
<td>94</td>
<td>102</td>
<td>118</td>
<td></td>
</tr>
<tr>
<td>LVMI, g/m²·7</td>
<td>36 (10)</td>
<td>43 (12)*</td>
<td>43 (12)†</td>
<td>47 (13)†</td>
<td>49 (11)†</td>
<td>54 (13)†</td>
<td>0.0001</td>
</tr>
<tr>
<td>RWT</td>
<td>0.42 (0.08)</td>
<td>0.46 (0.09)†</td>
<td>0.43 (0.08)</td>
<td>0.47 (0.09)†</td>
<td>0.46 (0.07)†</td>
<td>0.47 (0.09)‡</td>
<td>0.0001</td>
</tr>
<tr>
<td>EF</td>
<td>0.67 (0.08)</td>
<td>0.62 (0.14)†</td>
<td>0.67 (0.07)</td>
<td>0.66 (0.07)</td>
<td>0.64 (0.09)†</td>
<td>0.64 (0.07)‡</td>
<td>0.0041</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>1.01 (0.26)</td>
<td>1.23 (0.71)‡</td>
<td>0.93 (0.24)†</td>
<td>0.91 (0.25)‡</td>
<td>0.94 (0.27)*</td>
<td>0.93 (0.32)‡</td>
<td>0.0001</td>
</tr>
<tr>
<td>IVRT, ms</td>
<td>116 (20)</td>
<td>123 (26)</td>
<td>121 (21)‡</td>
<td>126 (22)‡</td>
<td>122 (17)*</td>
<td>128 (19)†</td>
<td>0.0001</td>
</tr>
<tr>
<td>MPI</td>
<td>0.57 (0.16)</td>
<td>0.66 (0.21)*</td>
<td>0.60 (0.15)</td>
<td>0.65 (0.17)†</td>
<td>0.62 (0.18)*</td>
<td>0.64 (0.14)‡</td>
<td>0.0005</td>
</tr>
</tbody>
</table>

Data are means (standard deviations). Normal weight is defined as BMI <25 kg/m²; overweight, BMI 25 to 30 kg/m²; obese, BMI >30 kg/m². All comparisons between the groups were adjusted for gender.

*P<0.05 vs normal weight without the MetS.
†P<0.0001 vs normal weight without the MetS.
‡P<0.01 vs normal weight without the MetS.
The only difference was that when using IR as the basis for grouping rather than the MetS, carotid artery IMT were thicker in the obese subjects without IR compared with the normal-weight individuals without IR (P=0.03).

Regarding the secondary hypothesis, overweight subjects without IR showed similar significant derangements in the CV and coagulation/fibrinolysis indices compared with normal-weight individuals without IR as when overweight subjects without the MetS were compared with normal weight without the MetS above. The only difference was that when using IR as the basis for grouping rather than the MetS, carotid artery compliance was reduced and MPI was impaired in the overweight subjects without IR compared with the normal-weight individuals without IR (P<0.05 for both) (for details, see Supplemental Tables I to III).

### Excluding Subjects With Diabetes and Prevalent CV Disorders

When excluding the 119 subjects in the sample with diabetes mellitus (defined as antidiabetic treatment or a fasting plasma glucose >7.0 mmol), history of myocardial infarction (n=53), stroke (n=24), or heart failure (n=21), subjects with obesity without MetS (now n=87) still showed reduced EDV and EIDV (both P<0.0001), EF (P=0.005), and E/A ratio (P=0.021) and increased LVMI and RWT (both P<0.0001), IVRT (P=0.016), MPI (P=0.019), tPA antigen (P<0.0001), fibrinogen (P=0.006), and PAI-1 activity (P<0.0001) compared with the normal-weight group without the MetS (now n=284).

The overweight group without the MetS (now n=277) also showed reduced EDV (P<0.0001), EIDV (P=0.001), IM-GSM (P=0.005), and E/A ratio (P=0.0001) and increased LVMI and RWT (both P<0.0001), IVRT (P=0.017), tPA antigen (P<0.0001), fibrinogen (P=0.015), and PAI-1 activity (P<0.0001) compared with the normal-weight group without the MetS. All comparisons between the groups were adjusted for gender.

A similar analysis excluding those with diabetes or a history of myocardial infarction, stroke, or heart failure, but using IR as classification instead of the MetS revealed that obese subjects without IR (n=96) still showed reduced EDV (P=0.001), EIDV (P=0.005), IM-GSM (P=0.048), EF (P=0.013), and E/A ratio (P<0.0001) and increased LVMI and RWT (both P<0.0001), IVRT (P=0.001), MPI (P=0.016), fibrinogen (P=0.001), tPA antigen, and PAI-1 activity (P<0.0001 for both) compared with the normal-weight group without the MetS (n=280).

The overweight group without IR (n=280) also showed reduced EDV and EIDV (both P<0.0001), IM-GSM (P=0.0001), and E/A ratio (P<0.0001) and increased LVMI (P<0.0001), IVRT (P=0.005), fibrinogen (P=0.014), and tPA antigen and PAI-1 activity (P<0.0001 for both) compared with the normal-weight group without the MetS. All comparisons between the groups were adjusted for gender.

### Discussion

In line with our primary hypothesis, our data do not support the notion of obesity without MetS being a harmless condition, because obesity without MetS was associated with impairments in multiple measures of subclinical CV disease as compared with normal-weight subjects without the MetS.

Furthermore, overweight subjects without the MetS also showed most of these impairments.

These findings were present both in the total sample and when excluding subjects with diabetes or manifest main CV disorders. The findings are in line with our recent publication showing an increased CV risk in both the obese subjects without the MetS and in overweight subjects without the MetS.17

### Definition of the MHO and Obesity

No uniform definition of MHO exists. Some previous investigators used insulin sensitivity measured by the hyperinsulinemic euglycemic clamp method to define MHO.9,10 Although this is a valid way to define MHO, it is not convenient in the clinical setting or in large-scale epidemiological research. We therefore used the National Cholesterol Education Program criteria to define the MetS, because this is a definition shown to be associated with future CV events, it is easy to apply, and it is correlated with measures of insulin.
sensitivity/resistance. Using this definition we obtained a slightly higher prevalence of MHO (10% versus 8%) than found in the community-based Framingham study. The fact that the Framingham cohort was on the average 17 years younger might explain a part of the difference. Researchers using the National Health and Nutrition Examination Survey databases found a similar prevalence of MHO (9.7%) but used a slightly different definition of the MetS.

The major question when defining MHO is how many metabolic disturbances one could accept. The most stringent answer would be that we should not allow any metabolic alterations. However, there was no obese subject in the present sample (out of 220) who did not show any of the MetS components. Furthermore, using the definition of Karolis et al, there were only 2 of 220 obese subjects who would be classified as MHO. Using the Iacobellis et al definition, none of the 220 obese subjects would be classified as MHO. Thus, assuming that MHO exists at all in the elderly, it is clear that none of these definitions could be used in the present sample. Therefore, we have chosen to use a BMI ≥30 kg/m² and occurrence of the MetS as our definition of MHO, but because we thereby allow some metabolic alterations in this group (see Table 1) we used the term “obesity without the MetS” and not “MHO” to be clear on the definition.

It can be argued that people with diabetes mellitus cannot belong to the MHO group. Therefore, we carried out an analysis excluding all diabetic subjects from the sample. Furthermore, because it could also be argued that prevalent CV disorders might confound the relationships between MHO and indices of subclinical CV disease, we also excluded those with the main CV disorders in this secondary analysis. This approach, however, did not change the conclusions of the study.

MHO and CV Characteristics
No previous studies have reported a detailed characterization of subclinical vascular and cardiac pathology in obesity without MetS. The finding that obesity without MetS was associated with increased LVM and RWT, impaired systolic and diastolic function, reduced vasoreactivity in forearm resistance vessels during infusion of both acetylcholine and nitroprusside, and impairments of several coagulation/fibrinolysis markers compared with the normal-weight subjects strongly suggest that obesity without MetS is not a benign condition.

Increased LVM, especially of the concentric type (with a high RWT) has previously been shown to predict CV events. Furthermore, impairments in both systolic function, such as EF, and diastolic function, such as the E/A ratio and IVRT, have been found to be markers of a poor prognosis. The MPI is a less commonly used echocardiographic index, but it is nevertheless a powerful predictor of mortality and future heart failure. Impaired vasoreactivity and coagulation/fibrinolysis are also known risk factors for future CV events, and an echolucent intima-media complex in the carotid artery is a powerful predictor of CV death. Hence, these observed CV changes in subjects with obesity without MetS could partly explain the increased risk for CV events reported in this group.

Generally, it is not clear why obesity induces subclinical CV alteration and further CV clinical events. One explanation could be by traditional risk factors, such as blood pressure, glucose, and lipids. In the present study, obese subjects without MetS showed slightly elevated levels of blood pressure and serum triglycerides and slightly lower levels of HDL than the normal-weight subjects without MetS. It is unlikely, however, that those mild disturbances would be the sole explanation for the rather pronounced alterations seen in many of the markers of subclinical CV disease investigated in the present study. It is therefore likely that some other signals originating from the adipose tissue, such as leptin, adiponectin, resistin, interleukin-6, or PAI-1, also are involved in the association between obesity without MetS and impairments in markers of subclinical CV disease.

Compared with the obese subjects with the MetS, the subjects with obesity without MetS generally showed less pronounced disturbances in the above mentioned CV characteristics. Therefore, the obese subjects with the MetS appear to be at a higher CV risk than the obese subjects without MetS, a finding that fits our recently published long-term follow-up data, but obesity without MetS should nevertheless not be considered a CV-healthy condition. The findings in the present study showing that obesity without MetS is at CV risk in between normal-weight without MetS and obese with MetS is further supported by previous findings that IMT in obesity without MetS is between that in normal-weight subjects without MetS and that in obese subjects with MetS.

Obesity has previously been associated with increased LVM, impaired vasoreactivity, and coagulation/fibrinolysis also in obese subjects without MetS would suggest that other mechanistic links exists between these CV alterations and obesity and would hopefully encourage future research to be more mechanistically oriented concerning these matters.

Overweight and CV Characteristics
Overweight subjects without the MetS, as well as subjects with obesity and without MetS, showed impairments in a number of CV characteristics compared with the normal weight. Thus, although these impairments were not as pronounced as those found in the MHO, overweight without the MetS should not be regarded as a benign condition. This is supported by our recent data showing that overweight subjects without the MetS also have an increased CV risk.

Metabolically Obese but Normal-Weight Individuals and CV Characteristics
It has become evident that the MetS also exists in nonobese individuals, and the term “metabolically obese but normal-weight” has been used to define this group. In these subjects, markers of visceral obesity and IR have been described, and the metabolically obese but normal weight experience an increased risk for CV disorders.
nately, we found a limited number of subjects who are metabolically obese but normal weight in our study (n=19), and therefore we do not have sufficient power to evaluate this group with any certainty.

**Insulin Resistance and Clinical Implications**

Because the concept of MHO initially was based measurements of IR and not the MetS, we also performed an analysis where we substituted the MetS with IR, based on HOMA index measurements. However, that approach resulted in almost identical results as when the MetS was used to define metabolic derangements.

The importance of diagnosing the MetS in clinical practice has been debated. Our data does not support the idea that characterization of the obese into 1 group with and 1 group without the MetS would identify 1 group as being CV healthy.

**Limitations of the Study**

The present sample is limited to whites aged 70. Caution should therefore be used in drawing conclusions about other ethnic and age groups.

The present study had a moderate participation rate. Therefore, we carried out an evaluation of CV disorders and medications in 100 consecutive subjects who denied participation. The prevalences of CV drug intake, history of myocardial infarction, coronary revascularization, antihypertensive medication, statin use, and insulin treatment were similar to those in the investigated sample, whereas the prevalences of diabetes, congestive heart failure, and stroke tended to be higher among the nonparticipants.

Many statistical tests were performed because we wanted to characterize the different groups as completely as possible from the CV perspective, so some false-positive results might have occurred by chance. Therefore, the results should be taken with caution until they are reproduced by others. It should, however, be emphasized that the findings in the present study regarding subclinical CV disease in obesity without MetS (and overweight without the MetS) are clearly consistent with our recently published data from an independent sample regarding long-term CV and mortality risk, making the findings in the present study likely to be true.

In conclusion, in contrast with some previous studies, our data do not support the notion of obesity without MetS being a benign condition, because obesity without MetS was associated with impairments in multiple markers of subclinical CV disease. This was also the case for overweight subjects without the MetS.

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**Disclosures**

None.

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28. Koren MJ, Devereux RB, Casale PN, Savage DD, Savage DD, Laragh JH. Relation of left ventricular mass and geometry to morbidity and mortality in uncomplicated essential hypertension. *Ann Intern Med*. 1991;114:345–352.


A Detailed Cardiovascular Characterization of Obesity Without the Metabolic Syndrome
Lars Lind, Agneta Siegbahn, Erik Ingelsson, Johan Sundström and Johan Årnlöv

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**Supplementary Table 1** Vascular characteristics in different BMI/insulin resistance (IR)-categories. IR was defined as the highest quartile of HOMA insulin resistance index (>2.6 mmol/l*mU/l). All comparisons between the groups were adjusted for gender.

<table>
<thead>
<tr>
<th></th>
<th>Normal weight Without IR</th>
<th>Normal weight With IR</th>
<th>Overweight Without IR</th>
<th>Overweight With IR</th>
<th>Obese Without IR</th>
<th>Obese With IR</th>
<th>ANOVA p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>308</td>
<td>34</td>
<td>330</td>
<td>108</td>
<td>113</td>
<td>111</td>
<td></td>
</tr>
<tr>
<td><strong>EDV (%)</strong></td>
<td>622 (344)</td>
<td>518 (252)</td>
<td>484 (267)d</td>
<td>459 (255)d</td>
<td>533 (389)b</td>
<td>399 (215)d</td>
<td>0.0001</td>
</tr>
<tr>
<td><strong>EIDV (%)</strong></td>
<td>427 (241)</td>
<td>369 (160)</td>
<td>353 (199)d</td>
<td>343 (191)c</td>
<td>345 (198)c</td>
<td>280 (167)d</td>
<td>0.27</td>
</tr>
<tr>
<td><strong>FMD (%)</strong></td>
<td>4.7 (3.6)</td>
<td>5.2 (3.7)</td>
<td>4.9 (3.5)</td>
<td>5.1 (3.5)</td>
<td>4.1 (3.7)</td>
<td>4.7 (4.0)</td>
<td></td>
</tr>
<tr>
<td><strong>IMT (mm)</strong></td>
<td>0.86 (0.15)</td>
<td>0.87 (0.13)</td>
<td>0.89 (0.17)a</td>
<td>0.91 (0.19)a</td>
<td>0.90 (0.15)a</td>
<td>0.93 (0.17)d</td>
<td>0.0029</td>
</tr>
<tr>
<td><strong>IM-GSM (units)</strong></td>
<td>85 (24)</td>
<td>76 (22)a</td>
<td>76 (22)d</td>
<td>76 (25)c</td>
<td>76 (23)c</td>
<td>74 (19)d</td>
<td>0.0001</td>
</tr>
<tr>
<td><em><em>CCA distensibility (1000</em>%/mmHg)</em>*</td>
<td>99 (51)</td>
<td>87 (40)</td>
<td>91 (44)a</td>
<td>90 (42)</td>
<td>89 (41)</td>
<td>86 (46)a</td>
<td>0.14</td>
</tr>
<tr>
<td><strong>SV/PP ratio (ml/mmHg)</strong></td>
<td>1.3 (0.5)</td>
<td>1.2 (0.3)</td>
<td>1.4 (0.5)</td>
<td>1.3 (0.5)</td>
<td>1.3 (0.5)</td>
<td>1.5 (0.5)a</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Data are means (standard deviations). Normal weight, body mass index <25 kg/m²; overweight, body mass index 25 kg/m²-30 kg/m²; obese, body mass index >30 kg/m².

a=p<0.05, b=p<0.01, c=p<0.001, d=p<0.0001 vs normal-weight without IR.

Abbreviations; EDV=endothelium-dependent vasodilation (invasive forearm technique), EIDV=endothelium-independent vasodilation (invasive forearm technique), FMD=flow mediated dilatation, CCA distensibility=distensibility of the common carotid artery, SV/PP=stroke volume to pulse pressure ratio, IMT=Intima media thickness of carotid artery, IM-GSM=echogenecity of the intima-media complex.
Supplementary Table 2 Left ventricular characteristics in different BMI/insulin resistance (IR)-categories. IR was defined as the highest quartile of HOMA insulin resistance index (>2.6 mmol/l*mU/l). All comparisons between the groups were adjusted for gender.

<table>
<thead>
<tr>
<th></th>
<th>Normal weight</th>
<th>Normal weight</th>
<th>Overweight</th>
<th>Overweight</th>
<th>Obese</th>
<th>Obese</th>
<th>ANOVA p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Without IR</td>
<td>With IR</td>
<td>Without IR</td>
<td>With IR</td>
<td>Without IR</td>
<td>With IR</td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>308</td>
<td>34</td>
<td>330</td>
<td>108</td>
<td>113</td>
<td>111</td>
<td></td>
</tr>
<tr>
<td>LVMI (g/m²²)</td>
<td>36 (10)</td>
<td>42 (13)c</td>
<td>44 (12)d</td>
<td>45 (13)d</td>
<td>48 (11)d</td>
<td>56 (13)d</td>
<td>0.0001</td>
</tr>
<tr>
<td>RWT</td>
<td>0.42 (0.08)</td>
<td>0.45 (0.09)</td>
<td>0.43 (0.08)</td>
<td>0.47 (0.09)d</td>
<td>0.46 (0.07)d</td>
<td>0.47 (0.08)d</td>
<td>0.0006</td>
</tr>
<tr>
<td>EF</td>
<td>0.67 (0.08)</td>
<td>0.62 (0.14)b</td>
<td>0.67 (0.07)</td>
<td>0.67 (0.07)</td>
<td>0.65 (0.09)b</td>
<td>0.64 (0.07)b</td>
<td>0.0001</td>
</tr>
<tr>
<td>E/A-ratio</td>
<td>1.03 (0.26)</td>
<td>1.04 (0.71)</td>
<td>0.93 (0.24)c</td>
<td>0.92 (0.25)c</td>
<td>0.92 (0.27)c</td>
<td>0.96 (0.32)a</td>
<td>0.0001</td>
</tr>
<tr>
<td>IVRT (ms)</td>
<td>116 (21)</td>
<td>120 (26)</td>
<td>122 (21)b</td>
<td>126 (22)d</td>
<td>124 (18)d</td>
<td>126 (19)d</td>
<td>0.0001</td>
</tr>
<tr>
<td>MPI</td>
<td>0.57 (0.16)</td>
<td>0.65 (0.21)a</td>
<td>0.60 (0.15)a</td>
<td>0.62 (0.17)</td>
<td>0.62 (0.19)b</td>
<td>0.64 (0.14)b</td>
<td>0.0062</td>
</tr>
</tbody>
</table>

Data are means (standard deviations). Normal weight, body mass index <25 kg/m²; overweight, body mass index 25 kg/m²-30 kg/m²; obese, body mass index >30 kg/m².

a=p<0.05, b=p<0.01, c=p<0.001, d=p<0.0001 vs normal-weight without IR

Abbreviations; left ventricular mass index (LVMI), Relative wall thickness (RWT), ejection fraction (EF), early rapid filling wave (E wave) and the peak velocity of atrial filling (A wave), isovolumic relaxation time (IVRT), myocardial performance index (MPI),
**Supplementary Table 3** Coagulation and fibrinolysis characteristics in different BMI/insulin resistance (IR)-categories. IR was defined as the highest quartile of HOMA insulin resistance index (>2.6 mmol/l*mU/l). All comparisons between the groups were adjusted for gender.

<table>
<thead>
<tr>
<th></th>
<th>Normal weight Without IR</th>
<th>Normal weight With IR</th>
<th>Overweight Without IR</th>
<th>Overweight With IR</th>
<th>Obese Without IR</th>
<th>Obese With IR</th>
<th>ANOVA p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D-dimer (ng/ml)</td>
<td>141 (144)</td>
<td>158 (144)</td>
<td>149 (138)</td>
<td>134 (233)</td>
<td>137 (100)</td>
<td>141 (124)</td>
<td>0.030</td>
</tr>
<tr>
<td>Fragment 1+2 (pmol/l)</td>
<td>235 (92)</td>
<td>212 (103)</td>
<td>226 (88)</td>
<td>214 (122)</td>
<td>235 (77)</td>
<td>204 (85)b</td>
<td></td>
</tr>
<tr>
<td>tPA antigen (ng/ml)</td>
<td>7.5 (3.3)</td>
<td>9.3 (3.3)b</td>
<td>9.0 (3.3)d</td>
<td>11.4 (3.7)d</td>
<td>10.4 (3.6)d</td>
<td>12.2 (3.6)d</td>
<td>0.0001</td>
</tr>
<tr>
<td>Von Willebrant factor (kIE/l)</td>
<td>1.3 (0.4)</td>
<td>1.4 (0.4)a</td>
<td>1.3 (0.4)</td>
<td>1.5 (0.5)d</td>
<td>1.4 (0.4)a</td>
<td>1.5 (0.5)d</td>
<td>0.0008</td>
</tr>
<tr>
<td>Fibrinogen (g/l)</td>
<td>3.4 (0.06)</td>
<td>3.5 (0.09)a</td>
<td>3.5 (0.06)a</td>
<td>3.6 (0.06)c</td>
<td>3.6 (0.06)b</td>
<td>3.8 (0.07)d</td>
<td>0.0001</td>
</tr>
<tr>
<td>PAI-1 activity (IU/ml)</td>
<td>5.0 (6.3)</td>
<td>10 (15)b</td>
<td>8.2 (10)d</td>
<td>15 (12)d</td>
<td>13 (15)d</td>
<td>25 (16)d</td>
<td>0.0001</td>
</tr>
<tr>
<td>Factor VIIa (U/l)</td>
<td>67 (27)</td>
<td>52 (29)</td>
<td>63 (27)</td>
<td>57 (33)a</td>
<td>65 (27)</td>
<td>62 (27)</td>
<td>0.012</td>
</tr>
</tbody>
</table>

Data are means (standard deviations). Normal weight, body mass index <25 kg/m²; overweight, body mass index 25 kg/m²-30 kg/m²; obese, body mass index >30 kg/m².
a=p<0.05, b=p<0.01, c=p<0.001, d=p<0.0001 vs normal-weight without the MetS.