

## Obesity is associated with coronary artery stenosis independently of metabolic risk factors: The population-based SCAPIS study

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### ABSTRACT

**Background and aims:** Previous studies reported divergent results on whether metabolically healthy obesity is associated with increased coronary artery calcium and carotid plaques. We investigated this in a cross-sectional fashion in a large, well-defined, middle-aged population using coronary CT angiography (CCTA) and carotid ultrasound.

**Methods:** In the SCAPIS study (50–65 years, 51% female), CCTA and carotid artery ultrasound were performed in 23,674 individuals without clinical atherosclerotic disease. These subjects were divided into six groups according to BMI (normal weight, overweight, obese) and the presence of metabolic syndrome (MetS) according to the NCEP consensus criteria.

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**Results:** The severity of coronary artery stenosis was increased in individuals with obesity without MetS compared to normal-weight individuals without MetS (OR 1.47, 95%CI 1.34–1.62;  $p < 0.0001$ ), even after adjusting for non-HDL-cholesterol and several lifestyle factors. Such difference was not observed for the presence of carotid artery plaques (OR 0.94, 95%CI 0.87–1.02;  $p = 0.11$ ). Obese or overweight individuals without any MetS criteria (except the waist criterion) showed significantly more pronounced stenosis in the coronary arteries as compared to the normal-weight individuals, while one criterion was needed to show increased plaque prevalence in the carotid arteries. High blood pressure was the most important single criterion for increased atherosclerosis in this respect.

**Conclusions:** Individuals with obesity without MetS showed increased severity of coronary artery stenosis, but no increased occurrence of carotid artery plaques compared to normal-weight individuals without MetS, further emphasizing that obesity is not a benign condition even in the absence of MetS.

## 1. Introduction

The term metabolically health obesity (MHO) was coined almost two decades ago to denote individuals with obesity but with no major metabolic risk factors for future disease [1–3]. In early studies on MHO, this group did not show any increased risk of future cardiovascular disease (CVD) events [4,5], but later studies with longer follow-up periods showed that MHO had only a delayed increase in risk compared to normal-weight individuals [6–9]. These observations are in line with reports that most subjects with MHO will develop cardiovascular risk factors with time [10–13], suggesting that MHO is just a transient condition in most cases. In addition, not only is MHO associated with increased risk of CVD, but an increased risk is also seen in metabolically healthy overweight [6]. Thus, the concept of MHO has been challenged [6,14].

If MHO is associated with an increased risk of CVD, MHO might also be linked to quantitative measures of atherosclerosis in different vascular beds. Indeed, in a meta-analysis published in 2020, MHO was associated with increased coronary atherosclerosis compared to normal-weight subjects when measured as coronary artery calcium score (CAC) [15], although this is not a universal finding in all studies. To note, CAC reflects coronary calcification and does not provide information on the degree of stenosis. The degree of stenosis has not yet been evaluated in MHO.

An increased amount of atherosclerosis in the carotid artery observed on ultrasound has been described in subjects with MHO compared to normal-weight subjects. A meta-analysis from 2014 found that four out of six studies showed an increased carotid artery intima-media thickness (IMT) in MHO subjects compared to normal-weight subjects [16]. Since then, several studies have reported increased signs of carotid atherosclerosis, most often measured as IMT, in MHO subjects [17–19], while one study did not find increased carotid artery atherosclerosis in MHO compared to normal-weight subjects [20]. However, no previous study has evaluated atherosclerosis both in the coronary and carotid arteries in the same population.

Thus, although the majority of published studies found increased atherosclerosis both in the coronary and carotid arteries linked to MHO, several studies did not. One reason for this discrepancy is that no uniform definition of MHO exists. The most common way to define metabolic disturbances is to use the national cholesterol education program (NCEP) consensus criteria for metabolic syndrome (MetS) [21], but in this case it is debatable how many of these criteria should be allowed in the definition of MHO and which of the risk factors included in MetS are most strongly associated with atherosclerosis.

The primary aim of the present study was to evaluate if the severity or amount of subclinical atherosclerosis in coronary and carotid arteries is increased in obese subjects without MetS compared to normal-weight subjects without MetS. For this purpose, we used the large population-based SCAPIS study in which coronary atherosclerosis was evaluated by coronary CT angiography (CCTA) with the degree of coronary artery stenosis as outcome [22]. The presence of atherosclerosis in the carotid arteries was determined by ultrasound. As secondary aim, we evaluated

if the severity or amount of atherosclerosis in the coronary or carotid arteries is increased in overweight subjects without MetS compared to normal-weight subjects without MetS. As third aim, we evaluated the different components used in the NCEP consensus criteria for MHO and their association with atherosclerosis in coronary and carotid arteries.

## 2. Patients and methods

### 2.1. Study sample

The Swedish CArdioPulmonary bioImage Study (SCAPIS) enrolled 30,154 individuals in the age-range of 50–65 years (51% women) in six cities in Sweden during 2013–2018. The participation rate was 50% of the invited individuals, and details on recruitment are given in Ref. [23]. The present study sample consisted of 23,674 subjects with both valid examinations of CCTA and carotid ultrasound, as well as risk factors included in MetS, following exclusion of 1066 subjects with either a self-reported history of myocardial infarction, stroke, angina pectoris, coronary revascularization, or diagnosed peripheral artery disease.

The study was approved by the Ethics Committee of Umeå University on behalf of all sites, and written informed consent was given by all participants.

### 2.2. Investigations

#### 2.2.1. Risk factors

Blood samples were drawn after an overnight fast. Glucose, total cholesterol, HDL-cholesterol, and triglycerides were measured by standard techniques at the different sites, and non-HDL-cholesterol was defined as total cholesterol minus HDL-cholesterol. Blood pressure was measured twice in both arms after 5 min rest in the supine position using an Omron M10-IT automated oscillometric device. The mean value of the two measurements from the arm with the highest mean level was used. Waist circumference (cm) was measured at the level of the iliac crest. Weight (kg) and height (m) were measured by standard techniques, and BMI was calculated ( $\text{weight}/\text{height}^2$ ).

#### 2.2.2. Lifestyle factors

Information on lifestyle factors and history of disease was obtained by a questionnaire.

Smoking was given on a three-level scale (never, previous, or current smoker). Alcohol intake was determined in grams/week. Exercise habits were given on a scale with five levels, 0 = never exercise, 1 = only occasionally exercise, 2 = 1–2 times a week, 3 = 2–3 time a week, and 4 = more than 3 times a week. Education was on a three-level scale (<10, 10–12, or >12 years in school).

#### 2.2.3. CCTA

Cardiac imaging in SCAPIS has been described in details previously [23]. Briefly, CT was performed using a dedicated dual-source CT scanner equipped with a Stellar Detector (Somatom Definition Flash, Siemens Medical Solution, Forchheim, Germany). In preparation for

CCTA imaging, renal function was assessed and potential contraindications were identified to exclude participants for whom the administration of contrast media could pose a risk. A  $\beta$ -blocker (metoprolol) and sublingual glyceryl nitrate were given for control of heart rate and dilation of coronary arteries. The contrast medium iohexol (GE Healthcare, 350 mg I/mL) was administered at a dose of 325 mg/kg body weight. CCTA was performed at 100 kV or 120 kV using five different protocols depending on heart rate, heart rate variability, presence of calcifications, and body weight.

After reconstruction of the images, all 18 coronary artery segments were visually examined for the presence of plaques, as previously described in detail [22]. The per-segment status of the coronary vessel was defined as no atherosclerosis; 1–49% stenosis; and  $\geq 50\%$  (i.e. significant) stenosis. Luminal obstruction was defined by visually estimating diameter stenosis using the average of the longest and shortest diameter at the site of stenosis. Each plaque was visually characterized as either calcified or non-calcified. Segments not assessable because of calcium blooming were coded as 1–49% stenosis, and segments with technical failures were coded as missing data. Individuals were classified based on the highest degree of stenosis present in the coronary artery circulation. In addition, as a sensitivity evaluation, the extent of atherosclerosis in the coronary tree was calculated for each individual as the sum of coronary segments with atherosclerosis (segment involvement score, SIS) [24].

All non-contrast image sets were reconstructed (B35f HeartView medium CaScore) and coronary artery calcium (CAC) was identified and scored using the syngo.via calcium scoring software (Volume Wizard; Siemens). Lesions exceeding the calcium threshold of 130 Hounsfield units in at least 3 neighboring pixels in a volume of  $1 \text{ mm}^3$  were identified with 3D-based picking and viewing tools. The area of calcification of each 3-mm slice was multiplied by an intensity factor and summed across slices for the whole coronary artery tree to a CAC score according to Agatston [25]. CAC scores (in Agatston Units) were used to define three groups; 0 (60% of the sample), 1–100 (28% of the sample),  $>100$  (12% of the sample).

#### 2.2.4. Carotid ultrasound

Atherosclerosis in the carotid arteries was determined using a standardized protocol with a Siemens Acuson S2000 ultrasound scanner equipped with a 9L4 linear transducer (both from Siemens Healthineers, Erlangen, Germany). The left and right carotid arteries were investigated, and atherosclerotic plaques in the common carotid artery, bulb, or internal carotid artery were identified. Plaques were defined as focal structures encroaching into the arterial lumen by at least 0.5 mm, or 50% of the surrounding IMT, or demonstrating a thickness  $>1.5$  mm as measured from the intima-lumen interface to the media-adventitia interface.

#### 2.2.5. Definitions of BMI/MetS subgroups

Three BMI-based groups were defined, namely normal weight,  $\text{BMI} < 25 \text{ kg/m}^2$ ; overweight,  $\text{BMI} 25\text{--}29.9 \text{ kg/m}^2$ , and obese,  $\text{BMI} \geq 30 \text{ kg/m}^2$ .

MetS and its five criteria were defined by the NCEP consensus criteria, including elevated waist circumference ( $\geq 94$  cm in men and  $\geq 80$  cm in women), elevated triglycerides ( $>1.7$  mmol/L), reduced HDL-cholesterol ( $<1.0$  mmol/L in men and  $<1.3$  mmol/L in women), elevated blood pressure (systolic  $\geq 130$  mmHg and/or diastolic  $\geq 85$  mmHg), and elevated fasting glucose ( $>5.6$  mmol/L) [21]. If three or more criteria were present, the subject was considered to suffer from MetS.

From these two characteristics (BMI and MetS), six subgroups could be defined: (a) normal weight without MetS, (b) normal weight with MetS, (c) overweight without MetS, (d) overweight with MetS, (e) obese without MetS, and (f) obese with MetS.

#### 2.2.6. Statistics

Two outcomes were evaluated, coronary stenosis and carotid plaque.

Coronary stenosis was defined on an ordinal scale with three levels of severity: 0 = no stenosis, 1 = 1–49% stenosis in any arterial segment or a calcified plaque, and 2 =  $\geq 50\%$  stenosis.

Carotid artery plaque was also defined on an ordinal scale with three levels: 0 = no plaque, 1 = plaque in one carotid artery, 2 = plaque in both carotid arteries.

We used a three-graded scale for both outcomes in order to obtain comparable estimates.

Ordinal logistic regression analysis was carried out for both outcomes. The exposure was the six BMI/MetS groups (nominal) with the normal weight without MetS group as the referent. Two degrees of adjustment were performed. The first adjustment was for age, sex, and study site (nominal), and the second adjustment was for non-HDL-cholesterol and the lifestyle factors of smoking, exercise habits, alcohol intake, and education level.

For the primary aim, the comparison between the obese group without MetS and the referent group was used. For the secondary aim, the comparison between the overweight group without MetS and the referent group was used. As sensitivity analysis for the primary and secondary aim, we also evaluated SIS because this measure of coronary atherosclerosis evaluates the amount of atherosclerosis rather than the degree of stenosis. In this respect, SIS resembles our measure of carotid artery plaque [24]. Also CAC was evaluated as a sensitivity analysis.

For the third aim, the obese and overweight groups were combined to improve the statistical power because both of these groups have been shown to have an increased risk of incident CVD [6].

In the first set of analysis regarding the third aim, the obese/overweight subjects were divided into groups according to the number of MetS criteria (excluding the waist criterion because almost all obese/overweight individuals fulfilled the waist criterion). These groups were evaluated vs. the referent group of normal weight without MetS. As above, ordinal logistic regression was carried out with two levels of adjustment for both coronary stenosis and carotid plaque.

In the second set of analysis regarding the third aim, only obese/overweight individuals with one MetS criterion (excluding the waist criterion) were grouped according to the type of criterion (blood pressure, glucose, HDL-cholesterol, and triglyceride levels) and evaluated vs. the referent group of normal weight without MetS. As above, ordinal logistic regression was carried out with two levels of adjustment for both coronary stenosis and carotid plaque.

In the third set of analysis regarding the third aim, the three groups defined by BMI were compared using adjustment for age, sex, systolic blood pressure, non-HDL-cholesterol, HDL-cholesterol, triglycerides, fasting glucose, smoking, alcohol intake, education, and exercise habits regarding risk of coronary artery stenosis.

For the primary and secondary objective, the *p*-value of significance was set to  $<0.025$  due to two outcomes. For the third aim, results with  $p < 0.05$  were reported as significant, since these analyses were mainly supportive to the first two aims.

STATA16 (Stata Inc, College Station, TX, USA) was used for all calculations.

### 3. Results

The basic participant characteristics are given in Table 1.

Proportions of atherosclerotic findings in the coronary and carotid arteries stratified by combinations of BMI and the MetS criteria are given in Fig. 1 and Supplementary Table 1.

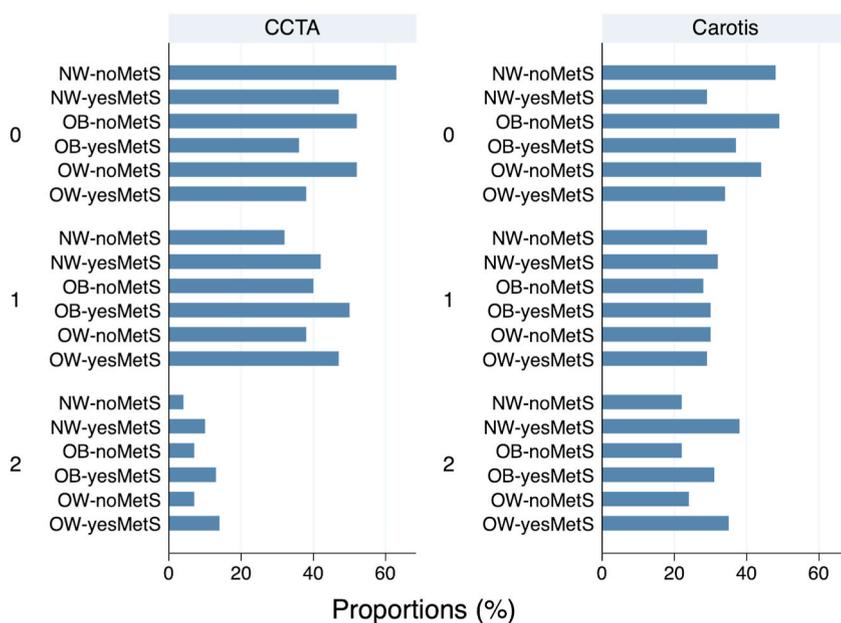
Atherosclerosis, evaluated as stenosis, in the coronary arteries was more common in men than in women ( $p < 0.0001$ ). 9.1% of men and 2.6% of women showed at least one  $\geq 50\%$  stenosis. The corresponding proportions of stenosis 1–49% were 48.9% in men and 29.3% in women.

Atherosclerosis in the carotid arteries was more pronounced in men than women ( $p < 0.0001$ ). 29.8% of men and 19.7% of women showed

**Table 1**  
 Characteristics of the sample divided by BMI groups and the presence of metabolic syndrome (MetS). Means and SD or proportions are shown.

	Normal weight without MetS	Normal weight with MetS	Overweight without MetS	Overweight with MetS	Obese without MetS	Obese with MetS	p-value for differences between groups
N	10,055	230	9640	2011	2930	2892	
Variable	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Age (years)	57.2 (4.3)	58.7 (4.3)	57.3 (4.3)	58.5 (4.1)	56.9 (4.2)	57.8 (4.3)	<0.0001
Women (%)	63	62	44	45	56	45	<0.0001
Systolic BP (mmHg)	120 [16]	134 [15]	125 [15]	135 [15]	127 [16]	135 [16]	<0.0001
Diastolic BP (mmHg)	73.8 (10.1)	81.9 (8.9)	77.4 (9.8)	82.3 (9.4)	80.0 (10.1)	83.9 (9.8)	<0.0001
Non-HDL-cholesterol (mmol/l)	3.64 (.98)	4.3 (1.27)	3.94 (1.02)	4.31 (1.19)	3.93 (.97)	4.16 (1.15)	<0.0001
HDL-cholesterol (mmol/l)	1.89 (.5)	1.27 (.43)	1.63 (.43)	1.24 (.36)	1.57 (.38)	1.2 (.31)	<0.0001
Triglycerides (mmol/l)	0.93 (0.45)	1.97 (1.03)	1.14 (0.58)	2.02 (1.06)	1.19 (0.47)	2.02 (1.27)	<0.0001
BMI (kg/m <sup>2</sup> )	22.7 (1.6)	23.8 (1.1)	27.0 (1.3)	27.8 (1.3)	32.9 (2.9)	34.0 (3.7)	<0.0001
Waist circumference (cm)	82.9 (7.7)	91.5 (6.2)	94.9 (7.2)	100.5 (6.8)	107.1 (9.4)	112.5 (9.9)	<0.0001
Fasting glucose (mmol/l)	5.3 (.7)	6.2 (1.7)	5.4 (.7)	6.2 (1.5)	5.5 (.7)	6.4 (1.8)	<0.0001
Diabetes diagnosis (%)	1.3	13	2.4	14	1.5	17	<0.0001
Antihypertensive treatment (%)	7.2	34	15	41	20	46	<0.0001
Statin treatment (%)	3.3	10.4	5.5	15	5.6	17	<0.0001
Antidiabetic treatment (%)	1.0	10.4	1.3	12.0	1.0	14.6	<0.0001
Alcohol (g/week)	6.7 (5.8)	6.8 (7.1)	7.7 (6.7)	7.5 (7.2)	6.7 (6.6)	6.9 (7.2)	<0.0001
Exercise habits levels (0 for sedentary and 4 for athlete)	0: 22% 1: 18% 2: 22% 3: 21% 4: 17%	0: 35% 1: 26% 2: 17% 3: 15% 4: 7%	0: 25% 1: 23% 2: 21% 3: 18% 4: 13%	0: 37% 1: 26% 2: 17% 3: 12% 4: 8%	0: 34% 1: 26% 2: 17% 3: 13% 4: 10%	0: 43% 1: 25% 2: 15% 3: 10% 4: 7%	<0.0001
Educational level	<10 years: 6% 10–12 years: 39% >12 years: 55%	<10 years: 8% 10–12 years: 53% >12 years: 39%	<10 years: 9% 10–12 years: 46% >12 years: 45%	<10 years: 12% 10–12 years: 50% >12 years: 38%	<10 years: 11% 10–12 years: 50% >12 years: 39%	<10 years: 15% 10–12 years: 54% >12 years: 31%	<0.0001
Smoking status	Never: 55% Previous: 33% Current: 12%	Never: 44% Previous: 33% Current: 23%	Never: 53% Previous: 36% Current: 11%	Never: 43% Previous: 38% Current: 19%	Never: 50% Previous: 40% Current: 10%	Never: 44% Previous: 41% Current: 15%	<0.0001
Number of metabolic syndrome components	.54 (.66)	3.17 (.43)	1.08 (.75)	3.33 (.56)	1.64 (.52)	3.52 (.67)	<0.0001
SIS	.77 (1.54)	1.48 (2.30)	1.06 (1.82)	1.68 (2.34)	1.07 (1.89)	1.67 (2.23)	<0.0001

SIS = segment involvement score. ANOVA or chi-square tests was used to evaluate if the groups were different.



**Fig. 1.** Proportions of atherosclerotic findings in the coronary (CCTA) and carotid arteries stratified by combinations of BMI and metabolic syndrome (MetS) criteria. NW = normal weight, OW = overweight, OB = obese. Both coronary artery stenosis and carotid plaque are on a three-level scale (0 = no stenosis, 1 = 1–49% stenosis, 2 = ≥50% stenosis for coronary artery stenosis and 0, 1, or 2 arteries with plaque for the carotid plaque). The number of subjects in each group is given in [Supplementary Table 1](#).

**Table 2**

Odds ratios (OR) for degree of coronary stenosis at coronary CT (upper part), carotid plaque (middle part), segment involvement score (SIS) and coronary artery calcium score (CAC) at coronary CT angiography for five groups of combinations of BMI and metabolic syndrome (MetS), with normal-weight subjects without MetS as the referent.

	Age, sex and site-adjusted		Multiple adjusted	
	OR (95%CI)	p-value	OR (95%CI)	p-value
<b>Coronary angiography stenosis</b>				
Normal weight without MetS	Reference group			
Normal weight with MetS	1.78 (1.33, 2.38)	<0.0001	1.48 (1.09, 2)	0.012
Overweight without MetS	1.17 (1.09, 1.24)	<0.0001	1.10 (1.03, 1.17)	0.0056
Overweight with MetS	2.10 (1.89, 2.34)	<0.0001	1.80 (1.61, 2.02)	<0.0001
Obese without MetS	1.47 (1.34, 1.62)	<0.0001	1.41 (1.28, 1.55)	<0.0001
Obese with MetS	2.41 (2.19, 2.64)	<0.0001	2.16 (1.96, 2.38)	<0.0001
<b>Carotid artery plaque</b>				
Normal weight without MetS	Reference group			
Normal weight with MetS	1.97 (1.55, 2.51)	<0.0001	1.68 (1.30, 2.16)	<0.0001
Overweight without MetS	1.03 (0.97, 1.08)	0.34	0.96 (0.91, 1.02)	0.19
Overweight with MetS	1.47 (1.35, 1.62)	<0.0001	1.23 (1.12, 1.35)	<0.0001
Obese without MetS	0.94 (0.87, 1.02)	0.11	0.87 (0.80, 0.95)	0.0013
Obese with MetS	1.35 (1.25, 1.47)	<0.0001	1.16 (1.07, 1.26)	<0.0001
<b>Sensitivity analysis</b>				
<b>SIS</b>				
Normal weight without MetS	Reference group			
Normal weight with MetS	1.78 (1.37, 2.31)	<0.0001	1.49 (1.14, 1.96)	0.0041
Overweight without MetS	1.15 (1.09, 1.22)	<0.0001	1.10 (1.03, 1.17)	0.0036
Overweight with MetS	1.89 (1.71, 2.08)	<0.0001	1.64 (1.48, 1.81)	<0.0001
Obese without MetS	1.35 (1.24, 1.47)	<0.0001	1.32 (1.21, 1.44)	<0.0001
Obese with MetS	2.05 (1.88, 2.22)	<0.0001	1.89 (1.73, 2.06)	<0.0001
<b>CAC</b>				
Normal weight without MetS	Reference group			
Normal weight with MetS	2.03 (1.56, 2.64)	<0.0001	1.72 (1.31, 2.26)	<0.0001
Overweight without MetS	1.15 (1.08, 1.22)	<0.0001	1.09 (1.02, 1.16)	0.0006
Overweight with MetS	1.87 (1.79, 2.17)	<0.0001	1.75 (1.58, 1.94)	<0.0001
Obese without MetS	1.41 (1.29, 1.53)	<0.0001	1.33 (1.22, 1.46)	<0.0001
Obese with MetS	2.31 (2.12, 2.51)	<0.0001	2.10 (1.92, 2.29)	<0.0001

The analyses were adjusted for age, sex, study site, or for these variables plus non-HDL-cholesterol, smoking, education level, alcohol intake, and exercise habits (multiple adjusted). Ordinal logistic regression was performed with both CT angiography stenosis and carotid plaque on a three-level scale (no stenosis, 1–49% stenosis, and  $\geq 50\%$  stenosis for CT angiography stenosis and 0, 1, or 2 arteries with plaque for the carotid plaque). SIS and is given on a 13-level scale. CAC is given on a three-level scale (0, 1–100, >100 Agatston units).

plaque in both carotid arteries.

### 3.1. Obesity without MetS vs. normal weight without MetS

As shown in Table 2, the severity of stenosis in the coronary arteries was increased in individuals with obesity without MetS compared to normal weight without MetS (OR 1.47 (95%CI 1.34–1.62),  $p < 0.0001$ ). This difference was still highly significant (OR 1.41 (95%CI 1.27–1.55),  $p < 0.0001$ ) after adjustment for non-HDL-cholesterol and lifestyle factors, as well as for some self-reported major concomitant non-CVD diseases (chronic obstructive pulmonary disease, 0.8% of the sample, rheumatoid diseases, 3.5% of the sample, any cancer diagnosis, 5.8% and inflammatory bowel diseases, 1.1% of the sample). This difference was still highly significant after further adjustment for statin use (7% of the sample, OR 1.36 (95%CI 1.24–1.50),  $p < 0.0001$ ). When we inserted menopausal status (15.7% of women premenopausal) as an additional confounder in a model only including women, the OR did not change (OR 1.39) and the  $p$ -value was still  $< 0.0001$ . Similar results were found when SIS or CAC were used (see Table 2 for details). In addition, the risk of having at least one calcified plaque (found in 42% of the sample) was increased in individuals with obesity without MetS compared to normal weight without MetS, following adjustment for non-HDL-cholesterol, statin use and lifestyle factors (OR 1.30 (95%CI 1.17–1.44),  $p < 0.0001$ ).

On the contrary, no significant increase in the amount of carotid atherosclerosis was seen in obese subjects without MetS in the age, sex and site-adjusted model (OR 0.94 (95%CI 0.87–1.02),  $p = 0.11$ , see Table 2 for details). However, following multiple adjustment, a significantly reduced risk of the amount of carotid atherosclerosis was seen (see Table 2).

When obese subjects without MetS were divided into those with ( $n = 1025$ ) or without hypertension ( $n = 1,905$ , hypertension defined as blood pressure  $\geq 140/90$  mmHg or regular antihypertensive treatment) and compared with the normal-weight without MetS following multiple adjustment, both groups showed increased risk of coronary artery stenosis (OR 1.22, 95%CI 1.08–1.38,  $p = 0.001$  in the non-hypertensive group and OR 1.78, 95%CI 1.53–2.06,  $p < 0.0001$ , in the hypertensive group). Thus, also obese subjects without MetS and without hypertension showed an increased risk of coronary artery stenosis. On the other hand, obese subjects without MetS and without hypertension showed a reduced risk of carotid atherosclerosis, while obese/overweight subjects without MetS and with hypertension showed a reduced risk of carotid atherosclerosis following multiple adjustment (OR 0.72, 95%CI 0.65–0.80,  $p < 0.0001$  in the non-hypertensive group and OR 1.22, 95%CI 1.08–1.38,  $p = 0.002$ , in the hypertensive group).

To evaluate if mild stenosis (1–49%) in the coronary arteries is also increased in individuals with obesity without MetS compared to normal weight without MetS, we excluded individuals with stenosis  $\geq 50\%$  from the sample in a *post-hoc* analysis. After this exclusion, a highly significant increased risk of atherosclerosis in the coronary arteries was seen in obese subjects without MetS (OR 1.41 (95%CI 1.30–1.55),  $p < 0.0001$ ).

No significant interactions between the two groups and age ( $p = 0.50$  and  $p = 0.33$ ) or between the two groups and sex ( $p = 0.82$  and  $p = 0.77$ ) were seen regarding atherosclerosis in the coronary or carotid arteries.

When the obese group without MetS was divided into subjects with class I obesity (BMI 30–34.99 kg/m<sup>2</sup>,  $n = 2369$ ), class II obesity (BMI 35–39.99 kg/m<sup>2</sup>,  $n = 455$ ) and class III obesity (BMI  $\geq 40$  kg/m<sup>2</sup>,  $n = 106$ ), all three groups showed an increased risk of coronary artery stenosis compared to the normal-weight group without MetS (OR 1.46 (95%CI 1.31–1.61) for class I, OR 1.59 (95%CI 1.28–1.98) for class II,

**Table 3**

Odds ratios (OR) for coronary CT angiography stenosis (upper part) and carotid plaque (lower part) for four groups of overweight or obese subjects with either 0 metabolic syndrome (MetS) criteria, 1 MetS criterion, 2 MetS criteria, or >2 MetS criteria (not including the waist criterion) with normal-weight subjects without any MetS criteria as the referent.

	Age, sex, and site-adjusted		Multiple adjusted	
	OR (95%CI)	p-value	OR (95%CI)	p-value
<b>Coronary angiography stenosis</b>				
Normal weight with 0 MetS criteria (n = 5921)	Reference group			
Obese/Overweight with 0 MetS criteria (n = 4734)	1.18 (1.07, 1.29)	0.00044	1.10 (1.01, 1.21)	0.037
Obese/Overweight with 1 MetS criterion (n = 6725)	1.70 (1.56, 1.84)	<0.0001	1.56 (1.43, 1.70)	<0.0001
Obese/Overweight with 2 MetS criteria (n = 3911)	2.20 (2.01, 2.42)	<0.0001	1.91 (1.73, 2.10)	<0.0001
Obese/Overweight with >2 MetS criteria (n = 2103)	3.42 (3.05, 3.84)	<0.0001	2.88 (2.55, 3.24)	<0.0001
<b>Carotid artery plaque</b>				
Normal weight with 0 MetS criteria (n = 5921)	Reference group			
Obese/Overweight with 0 MetS criteria (n = 4734)	0.96 (0.89, 1.04)	0.32	0.91 (0.84, 0.98)	0.011
Obese/Overweight with 1 MetS criterion (n = 6725)	1.37 (1.28, 1.47)	<0.0001	1.25 (1.17, 1.34)	<0.0001
Obese/Overweight with 2 MetS criteria (n = 3911)	1.55 (1.43, 1.68)	<0.0001	1.32 (1.21, 1.43)	<0.0001
Obese/Overweight with >2 MetS criteria (n = 2103)	2.06 (1.87, 2.27)	<0.0001	1.69 (1.53, 1.87)	<0.0001

The analyses were adjusted for age, sex, study site, or for these variables plus non-HDL cholesterol, smoking, education level, alcohol intake, and exercise habits. Ordinal logistic regression was performed with both CT angiography stenosis and carotid plaque on a three-level scale (no stenosis, 1–49% stenosis, and  $\geq 50\%$  stenosis for CT angiography stenosis and 0, 1, or 2 arteries with plaque for the carotid plaque).

and OR 1.52 (95%CI 0.97–2.39) for class III in the age and sex-adjusted analysis).

In a similar analysis with carotid atherosclerosis as outcome, none of the three obesity classes without MetS showed an increased risk vs the normal-weight group without MetS (OR 0.93 (95%CI 0.85–1.01) for class I, OR 0.97 (95%CI 0.81–1.17) for class II, and OR 0.97 (95%CI 0.68–1.40) for class III in the age and sex-adjusted analysis).

No significant sex-interactions were seen for the three obesity classes regarding the two atherosclerotic outcomes.

When the sample was stratified by sex, exercise habit was only a significant covariate in the relationship between stenosis at CCTA and normal-weight vs obesity without MetS in men ( $p < 0.0001$  for exercise habits in the model), but not in women ( $p = 0.92$  for exercise habits in the model). Despite this different impact of exercise in men and women, the increased risk of stenosis at CCTA seen between obesity without MetS and normal-weight without MetS was almost identical in men and women (OR 1.40 (95%CI 1.22–1.61 in men) and OR 1.39 (95%CI 1.21–1.60) in women).

### 3.2. Overweight without MetS vs. normal weight without MetS

As shown in Table 2, the severity of stenosis in the coronary arteries was increased in individuals with overweight without MetS compared to normal-weight without MetS (1.17 (95%CI 1.09–1.24),  $p < 0.0001$ ). This difference was highly significant also following adjustment for non-HDL-cholesterol and lifestyle factors, but was attenuated following further adjustment for statin use (1.06 (95%CI 0.99–1.13),  $p = 0.067$ ). Similar results were found when SIS was used. The risk of having at least one calcified plaque was not significantly increased in individuals with overweight without MetS compared to normal weight without MetS following adjustment for non-HDL-cholesterol, statin use and lifestyle factors ( $p = 0.26$ ).

No difference between the two groups was observed for carotid artery plaque ( $p = 0.34$ , Table 2). When individuals with stenosis  $\geq 50\%$  were excluded from the analysis, a significant increased risk of atherosclerosis in the coronary arteries was seen in obese subjects without MetS (OR 1.10 (95%CI 1.03–1.17),  $p = 0.006$ ).

### 3.3. MetS vs. non-MetS

Both the severity of stenosis in coronary arteries and the amount of atherosclerosis in carotid arteries was higher in subjects with MetS compared to subject without MetS irrespective of BMI ( $p < 0.0001$  for both outcomes, Table 2). No significant interactions were seen between MetS and BMI group regarding atherosclerosis in coronary or carotid

arteries.

### 3.4. Atherosclerosis vs. BMI

When BMI (as a continuous variable) was related to stenosis at CCTA, CAC and carotid plaque following adjustment for age and sex, very similar associations were seen for stenosis at CCTA and CAC (OR 1.056 for one unit change in BMI (95%CI 1.050–1.063) for stenosis at CCTA and OR 1.051 (95%CI 1.045–1.056) for CAC,  $p < 0.0001$  for both). BMI was also related to carotid artery plaque, but the association was less powerful OR 1.007 (95%CI 1.002–1.012) for CAC,  $p = 0.005$ ).

### 3.5. Obesity and overweight vs. normal weight following risk factor adjustment

When overweight or obese subjects were compared with normal-weight individuals following adjustment for age, sex, systolic blood pressure, non-HDL-cholesterol, HDL-cholesterol, triglycerides, fasting glucose, smoking, alcohol intake, education, and exercise habits, obese individuals (OR 1.36 (95%CI 1.25–1.48),  $p < 0.001$ ) but not overweight subjects (OR 1.06 (95%CI 0.99–1.13),  $p = 0.08$ ) showed an increased risk for stenosis in coronary arteries.

### 3.6. Number of MetS components

For coronary atherosclerosis, obese or overweight individuals without any MetS criteria (except the waist criterion) showed significantly more severe stenosis in the coronary arteries compared to normal weight individuals without MetS (Table 3). This was also seen after adjustment for non-HDL-cholesterol and lifestyle factors. The severity of coronary atherosclerosis increased with the number of MetS criteria.

For carotid atherosclerosis, obese or overweight individuals without any MetS criteria (except the waist criterion) did not show significantly more pronounced atherosclerosis as compared to normal-weight individuals without MetS criteria, but overweight individuals with one MetS criterion did (Table 3). In addition, the extent of carotid atherosclerosis increased with the number of MetS criteria.

### 3.7. Impact of the different MetS criteria

When obese or overweight individuals with one MetS criterion (except the waist criterion) were compared with normal-weight individuals without MetS criteria, the severity of coronary stenosis was increased for all four criteria (blood pressure, glucose, HDL, and triglycerides, Table 4). Following adjustment for non-HDL-cholesterol and

**Table 4**

Odds ratios (OR) for coronary CT angiography stenosis (upper part) and carotid plaque (lower part) for four groups of overweight or obese subjects with one metabolic syndrome (MetS) criteria – either the blood pressure, glucose, HDL, or triglyceride level – with normal-weight subjects without any MetS criteria as the referent.

	Age, sex, and site-adjusted		Multiple adjusted	
	OR (95%CI)	p-value	OR (95%CI)	p-value
<b>Coronary angiography stenosis</b>				
Normal weight without MetS	Reference group			
Blood pressure criterion	1.84 (1.69, 2.02)	<0.0001	1.72 (1.56, 1.89)	<0.0001
Glucose criterion	1.41 (1.17, 1.70)	0.00030	1.39 (1.14, 1.69)	0.00096
HDL criterion	1.30 (1.06, 1.59)	0.011	1.15 (0.94, 1.42)	0.18
Triglyceride criterion	1.45 (1.22, 1.71)	0.000020	1.01 (0.84, 1.21)	0.95
<b>Carotid artery plaque</b>				
Normal weight without MetS	Reference group			
Blood pressure criterion	1.52 (1.41, 1.64)	<0.0001	1.42 (1.31, 1.54)	<0.0001
Glucose criterion	0.97 (0.82, 1.14)	0.67	0.97 (0.82, 1.14)	0.69
HDL criterion	1.11 (0.94, 1.31)	0.21	0.98 (0.83, 1.16)	0.82
Triglyceride criterion	1.18 (1.02, 1.36)	0.026	0.86 (0.74, 1.01)	0.060

The analyses were adjusted for age, sex, and study site or for these variables plus non-HDL-cholesterol, smoking, education level, alcohol intake, and exercise habits. Ordinal logistic regression was performed with both CT angiography stenosis and carotid plaque on a three-level scale (no stenosis, 1–49% stenosis, and  $\geq 50\%$  stenosis for CT angiography stenosis and 0, 1, or 2 arteries with plaque for the carotid plaque).

lifestyle factors, only blood pressure and glucose criteria remained significant.

For carotid arteries, blood pressure and triglyceride criteria were significantly related to increased atherosclerosis burden when obese or overweight individuals with one MetS criterion (except the waist criterion) were compared with normal-weight individuals without any MetS criteria. Following adjustment for non-HDL-cholesterol and lifestyle factors, only the blood pressure criterion remained significant.

#### 4. Discussion

The present cross-sectional, observational study showed that the severity of coronary artery stenosis, but not the extent of carotid artery plaques, was increased in obese subjects without MetS compared to normal-weight subjects without MetS.

##### 4.1. Coronary stenosis

Previous studies evaluating the impact of MHO on subclinical coronary artery disease have used CACS [15]. This is a valid measure of coronary artery atherosclerosis that predicts major adverse coronary events in both high-risk and low-risk individuals [26,27]. Our results confirm and importantly extend previous observations using CACS in which two out of three cross-sectional studies [13,28,29] showed an increased risk of having calcifications in the coronary arteries in MHO. In the present study, CCTA was used to define coronary artery disease. CCTA provides information on the degree of stenosis not given by CACS, and we have previously shown the complementary value of CCTA compared with CACS in a population sample [22]. Obese subjects without MetS had increased severity of stenosis in the coronary arteries compared to normal-weight subjects without MetS in a large population-based sample of subjects without any clinically manifest atherosclerotic disease. This relationship was highly significant, and adjustment for non-HDL-cholesterol, statin use and lifestyle factors had only a minor impact on the strength of the associations. A sensitivity analysis also showed that obese and subjects without MetS had an increased risk of mild stenosis (1–49%), suggesting that increased BMI might have a role in the early formation of coronary artery plaques. Very similar results were seen when we used SIS or the presence of calcified plaque in sensitivity analyses.

In the age-sex-adjusted models, also overweight individuals without MetS showed increased severity of stenosis in the coronary arteries compared to normal-weight subjects without MetS, but this relationship was markedly attenuated following adjustment for non-HDL-cholesterol, statin use and lifestyle factors. Furthermore, it could be noted that when overweight subjects were compared to normal-weight

individuals, no significant differences ( $p = 0.08$ ) regarding the severity of stenosis in the coronary arteries between the groups were seen when adjusting for the risk factors included in MetS plus lifestyle factors. Such a difference was seen between obese subjects and normal-weight individuals.

##### 4.2. Carotid plaque

Most of the previous studies evaluating the impact of MHO on carotid artery atherosclerosis have used IMT, but some studies have used atherosclerotic plaques as the outcome [19,20]. These two studies show divergent results regarding whether or not MHO is associated with increased plaque prevalence compared to normal-weight individuals. In the present study, we could find no such association, suggesting that obesity without MetS is more deleterious for atherosclerosis in coronary arteries than in carotid arteries. It has also previously been shown that MetS does not increase the risk of re-stenosis following carotid endarterectomy [30].

One explanation for the lack of increased risk of carotid artery plaque in obesity without MetS could be the definition we used for plaque being a focal thickening of the intima. This definition relies on the visual detection of plaque, usually located in the bulb area, while IMT in most studies is measured in the common carotid artery. In obese subjects, proper visualization of the bulb is often more difficult than visualization of the far wall of the common carotid artery. Plaques in the bulb area might therefore be missed in obese individuals, especially the echolucent plaques. In an unpublished *post-hoc* analysis, we used data from the PIVUS study (a population-based study with 1016 individuals all aged 70 years, 50% women) [31] to assess this phenomenon. In that study, we did not find BMI to be related to plaque occurrence when defined as 50% greater focal thickening of the common carotid artery intima compared to the surrounding parts (OR 0.97 (95%CI 0.94–1.01),  $p = 0.20$ ), while BMI was related to plaque in a highly significant manner when IMT in the common carotid artery was defined as  $\geq 1.2$  mm (OR 1.06 (95%CI 1.03–1.10),  $p < 0.001$ ). Thus, the presently used definition of plaque in the SCAPIS study might have underestimated the risk of carotid atherosclerosis in obese and overweight subjects due to differences in plaque definitions and problems in identifying plaque in those subjects. Unfortunately, we do not yet have measurements of IMT in the SCAPIS cohort that can be used to corroborate the findings in the PIVUS study.

It is not likely that the lack of increased risk of carotid atherosclerosis is due to a limited power, since a power analysis using Pearson's chi-squared test showed a  $>99\%$  power to detect an OR of 2.0 when obese subjects without MetS were compared with normal-weight subjects without MetS (primary aim) at a significance level of 0.0001.

#### 4.3. Definition of metabolically healthy obesity (MHO)

There is a critique of MetS as being inadequate, since the different components are a manifestation of obesity and the risk of CVD for MetS in itself is not greater than the sum of its components [32]. However, almost all of the knowledge on how MHO is linked to incident CVD comes from studies using MetS [5,6,9]. Thus, although not the ideal definition of the clustering of risk factor in the same individuals, we have used MetS to explore subclinical atherosclerosis to make our results comparable to previous studies using incident CVD as outcome.

There are several definitions of MHO. Most investigators use the NCEP MetS criteria, while others include measurements of insulin resistance [1], but other definitions also exist [33]. Because we did not measure fasting insulin in the SCAPIS cohort, we cannot compare those two approaches, but we have previously shown that when MHO was defined by MetS and by insulin resistance, MHO showed an increased risk of future CVD [6]. It is, however, of interest to evaluate how MHO should be defined using the MetS criteria. In such an evaluation, we have previously shown that the risk of future clinical CVD increased in obese subjects even if no other MetS criteria were present. In the overweight subjects, one MetS criterion was needed for an increased risk of clinical CVD [34]. In agreement with these findings, in the current study we saw an increased risk of severe coronary stenosis in obese subjects even if no other MetS criteria were present. For carotid plaque, one MetS criterion was needed to be at increased risk. Moreover, the separate analysis adjusting for each of the risk factors as continuous variables showed that obese individuals had an increased risk of stenosis in the coronary arteries.

#### 4.4. Type of risk factor

There might be a difference between risk factors regarding coronary and carotid atherosclerosis in obese or overweight subjects. Because the occurrence of one risk factor clearly increased the risk of both coronary and carotid atherosclerosis, we evaluated which of the different MetS criteria were of importance for each vascular bed. There was a clear difference between coronary and carotid arteries in that blood pressure was related to atherosclerosis in both arterial beds, while the glucose criterion was only related to increased risk of coronary stenosis after multiple adjustment. Thus, of the MetS criteria, blood pressure was the most deleterious in terms of atherosclerosis in obese or overweight subjects, followed by glucose. Importantly, these results are in agreement with our analyses of the association between different MetS criteria and future clinical CVD [34]. It should, however, be acknowledged that obesity/overweight could induce hypertension; therefore, it is plausible that hypertension is a mediator in the causal pathway between obesity/overweight and atherosclerosis and it should be regarded as it is the combination of obesity/overweight that is linked to atherosclerosis.

#### 4.5. Differences between the measurements of carotid and coronary atherosclerosis

CCTA was in the current study mainly used to evaluate stenosis of the coronary arteries and degree of calcification, while plaque volume can only be measured after more detailed image analyses. B-mode ultrasound focused on measuring number and localisation of carotid plaques while degree of stenosis was measured separately using Doppler. Thus, it should be acknowledged that we evaluated different facets of atherosclerosis in the two artery beds assessed. Whether or not this fact could explain the discrepant findings for the two arteries regarding the main aim of the study is not known.

#### 4.6. Clinical implications

Although there are no randomized clinical trials (RCT) performed in

asymptomatic patients with coronary artery stenosis >50%, it seems likely that this group would benefit from aggressive lipid lowering, as in patients with acute coronary syndrome [35]. Since we find coronary artery stenosis to be more common in obese subjects, regardless of whether MetS is present or not, it is likely that lipid-lowering therapy should be more liberally applied in obese subjects, but this assumption has to be evaluated in a RCT.

According to international guidelines, CCTA is the number one recommended non-invasive diagnostic method in patients with low to medium probability of CAD, a group which includes the vast majority of women. Although the risk of coronary artery stenosis was increased in asymptomatic individuals with obesity, it is not likely that subjects with obesity, especially if not associated with other risk factors, would benefit from a general screening by CCTA. Women showed a similar increase in relative risk to men, but the absolute risk is substantially lower in the age-group investigated in the present study.

#### 4.7. Strength and limitations

The major strength of the present study is that both the degree of coronary stenosis and the amount of carotid plaque were measured with gold standard methods in a large population-based sample.

In this study, CCTA was performed at six sites and for practical reasons a limited reader protocol was used for evaluation of degree of stenosis to increase success rate and reproducibility of data (details presented in reference 22). It is acknowledged that an automated/semiautomated evaluation would have been preferred, but we have not yet been able to achieve this goal in 25,000 individuals.

Because our sample consisted of Swedish subjects with almost exclusively European descent, the results need to be reproduced in other ethnic and geographical groups. Recent data show that there are no associations between MetS and extracranial carotid artery stenosis in Chinese subjects [36].

Because the SCAPIS study was only recently completed, we do not yet have outcome data regarding the incidence of myocardial infarction and stroke that could put the findings regarding atherosclerosis into a clinical end-point perspective. The lack of data on IMT is another limitation.

In the present study, we have measured blood pressure in the supine position, according to Swedish standards, while we are aware that many other studies use sitting pressure. The difference in blood pressure between the methods after some time at rest would be marginal and is unlikely to change the results to any important degree.

More modern and accurate techniques than questionnaire data to quantify exercise habits, such as accelerometry, are today present. The impact of exercise habits as a confounder might have been slightly underestimated in the present study.

Since this was an observational study, causality could not be claimed for the associations presented. However, given that an intervention study in obesity, although not randomized, showed a profound risk reduction in incident atherosclerotic events and cardiovascular death in those with weight loss compared to controls [37], and given that Mendelian randomization studies have shown genetic links between high BMI and coronary artery disease [38], it is more likely that high BMI will induce coronary atherosclerosis than the reverse, with hypertension as a main mediator of risk.

It was not an aim of this investigation to study the small group being normal-weight with MetS, and we did not comment on the results in this group even if they are given in sake of completeness. So, the given results for this group should be taken with caution, since the present sample is underpowered to study it in a reliable fashion.

#### 4.8. Conclusion

Individuals with obesity without MetS showed increased severity of coronary artery stenosis, but not increased extent of carotid artery

plaque, compared to normal-weight individuals without MetS. Our data further emphasize that MHO is not a benign condition.

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### Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.atherosclerosis.2022.10.007>.

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