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Associations of metabolically healthy obesity with prevalence and progression of coronary artery calcification: Results from the Heinz Nixdorf Recall Cohort Study

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Subclinical atherosclerosis;
Cohort study

Abstract *Background and aims:* There is controversy on the potentially benign nature of metabolically healthy obesity (MHO), i.e., obese persons with few or no metabolic abnormalities. So far, associations between MHO and coronary artery calcification (CAC), a measure of subclinical atherosclerosis, have mainly been studied cross-sectionally in Asian populations. We assessed cross-sectional and longitudinal MHO CAC associations in a Caucasian population.

Methods and results: In the Heinz Nixdorf Recall Study, a population-based cohort study in Germany, CAC was assessed by electron-beam tomography at baseline and at 5-year follow-up. For cross-sectional and longitudinal analyses, we included 1585 participants free of coronary heart disease at baseline, with CAC measurements at baseline and at follow-up, and with either normal weight (BMI 18.5–24.9 kg/m^2) or obesity (BMI $\geq$30.0 kg/m^2) at baseline. We used four definitions of MHO. In our main analysis, we defined obese persons as metabolically healthy if they met $\leq$1 of the NCEP ATP III criteria for the definition of the metabolic syndrome – waist circumference was not taken into account because of collinearity with BMI.

Persons with MHO had a higher prevalence of CAC than metabolically healthy normal weight (MHNW) persons (prevalence ratio = 1.59 (95% confidence interval 1.38–1.84) for the main analysis). Persons with MHO had slightly larger odds of CAC progression than persons with MHNW (odds ratios ranged from 1.17 (0.69–1.99) to 1.48 (1.02–2.13) depending on MHO definition and statistical approach).

Conclusion: Our analyses on MHO CAC associations add to the evidence that MHO is not a purely benign health condition.

Abbreviations: CAC, coronary artery calcification; CI, confidence interval; CVD, cardiovascular disease; MHO, metabolically healthy obesity; MUO, metabolically unhealthy obesity; MUNW, metabolically unhealthy normal weight; MHNW, metabolically healthy normal weight; OR, odds ratio; PR, prevalence ratio; WC, waist circumference.

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Introduction

Obesity is a strong risk factor for cardiovascular disease (CVD) [1,2]. But as obesity is also strongly associated with CVD risk factors like dyslipidemia, hypertension and dysglycemia [3], it is of interest whether obese persons with few or no such metabolic abnormalities still have an increased CVD risk. For these persons the term "metabolically healthy obese" (MHO) has been coined, but there is controversy on the definition and potential benign nature of this condition [4,5]. The authors of two recent meta-analyses both concluded that in persons with MHO, CVD risk was larger than in persons with metabolically healthy normal weight (MHNW), but not as large as in persons with metabolically unhealthy obesity (MUO) and metabolically unhealthy normal weight (MUNW) [6,7]. However, one of these meta-analyses only included non-adjusted effect estimates [6].

So far, there has been little research on the association between MHO and subclinical atherosclerosis. Coronary artery calcification (CAC) is a measure of subclinical atherosclerosis, and, moreover, an established risk factor of cardiovascular events [8,9]. Furthermore, CAC has been shown to be a risk factor even for all-cause mortality [10]. There are few cross-sectional studies on the MHO CAC association, which have all but one been done in Asian populations with Asian-specific cut-offs to define obesity [11–15]. Khan et al. found in a female midlife population that the proportion of CAC prevalence was larger in MHO than in MHNW [11]. In two further studies, MHO persons had a larger prevalence of CAC proportion than MHNW persons, but lower CAC prevalence than metabolically unhealthy persons [12,13]. Contrary to the two aforementioned studies, Sung et al. found no larger CAC prevalence in MHO, and Chang et al. reported that persons with MHO had only a fairly small increase in CAC prevalence after adjustment for components of the metabolic syndrome [14,15]. In 2017, the first two longitudinal studies on the MHO CAC association were published, again in Asian populations with BMI $\geq$25 kg/m^2 as cut-off for obesity [16,17]. In one study, results depended on the MHO definition, and considering persons with $\leq$1 metabolic abnormality as metabolically healthy, the risk of CAC progression was larger in MHO than in MHNW (relative risk (RR) = 1.65 (95% confidence interval (CI) 1.14–2.39)) [16]. In the second longitudinal study, the odds ratio for the relation between presence of MHO phenotype and CAC progression was 1.45 (95% CI: 0.93–2.25).; however, after stratification by presence of fatty liver disease, a strong MHO CAC association was only seen in persons with fatty liver disease [17].

Our objective is to use prospective data from the population-based Heinz-Nixdorf Recall Study to assess cross-sectional and longitudinal MHO CAC associations in a Caucasian population. In addition, we compare the risk of persons with MHO and MHNW, respectively, to convert to a metabolically unhealthy status during follow-up.

Methods

Study population

The Heinz Nixdorf Recall (HNR) Study is a population-based prospective cohort study conducted in three large adjacent cities (Bochum, Essen, Mülheim) in the Ruhr-region in Germany. The study rationale and design have been described in detail elsewhere [18]. In brief, the cohort comprises a total of 4814 participants (49.8% men, aged 45–76 years). The baseline visits were performed between 2000 and 2003, the 5-year follow-up visits between 2005 and 2008, with a median follow-up of 5.1 years. The 5-year follow-up response was 90.2%. Data assessment at baseline and 5-year follow-up included a self-administered questionnaire, face-to-face interviews, and a physical examination including among others anthropometric measurements and comprehensive laboratory tests. As the focus of our study is on comparing (metabolically healthy) obese persons with (metabolically healthy) normal weight persons, persons with overweight (BMI 25.0–29.9 kg/m^2) or underweight (BMI $<$ 18.5 kg/m^2) were excluded from analyses. 1585 subjects formed the analysis set (cf. flow-chart in Fig. 1). When normal weight and obesity were defined by waist circumference (WC) instead of BMI in additional analyses, the analysis set included 2125 subjects.

The study was approved by the Ethics Committee of the Medical Faculty of the University Clinic Essen. All participants gave their written informed consent.

Definition of MHO

To define metabolic health, we used the criteria of the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) for the definition of the metabolic syndrome [19]: (1) systolic blood pressure $\geq$130 mmHg or diastolic blood pressure $\geq$85 mmHg or use of antihypertensive medication; (2) HDL cholesterol $<$40 mg/dl (men)/$<$50 mg/dl (women) or drug treatment for reduced HDL cholesterol; (3) triglycerides $\geq$150 mg/dl or drug treatment for elevated triglycerides; (4) prevalence of diabetes or fasting glucose $\geq$100 mg/dl. Waist circumference was not taken into account because of collinearity with BMI. To state drug treatment for elevated triglycerides or reduced HDL cholesterol, intake of fibrates and nicotinic acid was taken into account according to the Joint Interim Statement of the International Diabetes Federation Task [19]. With regard to the 4th criterion, diabetes was diagnosed if participants gave a self-report of a physician's diagnosis, or if antidiabetic drugs were taken. We used 4 h as a cut-off for the fasting state because an earlier study had shown that glucose levels hardly decline any more after fasting more than 4 h [20].

In our main analysis (MHO definition 1), persons were defined as metabolically healthy if they met $\leq$1 of the four aforementioned NCEP ATP III criteria (MHO definition 1). We used BMI $\geq$30 kg/m^2 as obesity cut-off. According to status of metabolic health (yes/no) and presence of obesity (yes/no), participants were grouped into four categories: MHO, MUO, MUNW, and MHNW.

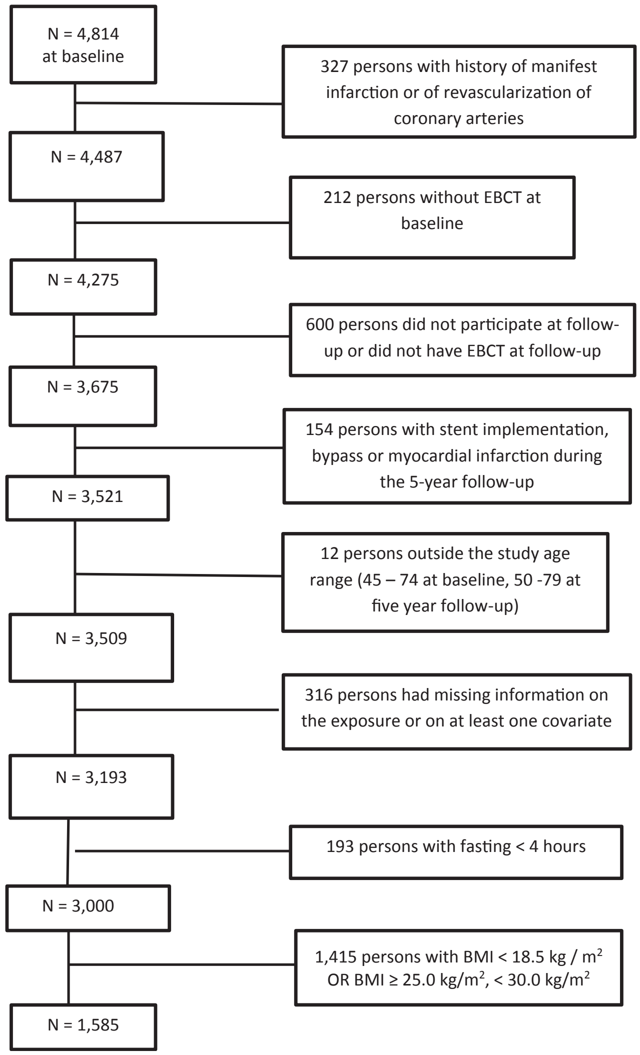

Figure 1 Flow-chart of persons entering the data analysis set.

In addition to our main analysis, we used three further definitions of MHO:

MHO definition 2 was like MHO definition 1, but persons were only defined as metabolically healthy if they met none of the aforementioned NCEP ATP III criteria.
MHO definition 3 was like MHO definition 1, but hsCRP ≥0.3 mg/dl was included as an additional metabolic abnormality.
MHO definition 4 was like MHO definition 1, but obesity was defined by waist circumference instead of BMI (≥102 cm in men/≥88 cm in women).

In the supplementary material (Table 1), we provide an overview of our four MHO definitions.

Statistical analyses

We used robust Poisson regression [21] to estimate prevalence ratios (PRs) and 95% confidence intervals (CIs) for the association between MHO and presence of CAC.

Several statistical approaches to model CAC progression have been suggested [22]. We used two different regression approaches to assess the association between MHO and CAC progression:

1. CAC at the 5-year examination was modeled from age- and sex-specific CAC percentiles at baseline, exponentially extrapolating along the subject's percentile by the time interval between measurements [23]. A predefined acceptance band nominally covers 20% of observed values around the individually predicted value at 5 years. CAC progression classified as within band (expected), above band (rapid), below band (slow) was used as the outcome variable (reference: expected) in multinomial logistic regression models. In other words, "rapid" ("slow") means faster (slower) than expected from an extrapolation of baseline CAC values.
2. From absolute CAC changes (CAC at follow-up minus CAC at baseline), a categorical variable for annual CAC change (≥100 Agatston units; 10–99 Agatston units; <10 Agatston units (reference)) was created which was used as the dependent variable in ordinal logistic regression analyses. The proportional odds assumption was fulfilled for these analyses.

PRs and ORs were reported for crude models (model 1). Adjustment for potential confounders was performed for age, sex, smoking, physical activity and school education (model 2).

We calculated the proportion of persons with MHO and MHNW who were not metabolically healthy any more at 5-year follow-up. We estimated the corresponding relative risk from modified Poisson regression models with robust variance [21], with adjustment for age, sex, smoking, physical activity, and school education.

All statistical analyses were performed using SAS version 9.4.

Baseline measurement of components of metabolic syndrome and of covariates and assessment of CAC are available as supplementary material.

We are calculating and reporting confidence intervals to assess the precision of our estimates because our goal is estimation and not significance testing. We wish to avoid publication bias by preferential reporting of significance results. Instead, we judge the value of our estimates by their precision and validity.

Results

The proportion of obese persons who were metabolically healthy ranged from 4.1% (MHO definition 2) to 25.6% (MHO definition 4). Regardless of the MHO definition used, MHO subjects had a less favorable metabolic profile than MHNW subjects with regard to systolic and diastolic blood pressure, lipid concentrations, and HbA1c (Table 1; supplementary Table 2). Moreover, persons with MHO were older than persons with MHNW, more often had low school education, had a larger waist circumference, and a larger intake of antihypertensive medication.

Table 1 Baseline characteristics of study participants by groups of metabolic health (definition 1) and obesity: the Heinz Nixdorf Recall Study.[a,b]

	Normal weight		Obese	
	BMI 18.5–24.9 kg/m^2		BMI ≥ 30 kg/m^2	
	Metabolically healthy[a]	Metabolically unhealthy[a]	Metabolically healthy[a]	Metabolically unhealthy[a]
N	486	347	159	593
Age (years)	56.5 ± 7.2	58.5 ± 7.3	58.3 ± 7.9	60.4 ± 7.5
Sex (Male) (%, (n))	24.9 (121)	45.8 (159)	26.4 (42)	48.7 (304)
BMI (kg/m^2)	22.7 ± 1.5	23.3 ± 1.4	32.8 ± 2.7	33.5 ± 3.3
WC (cm)	78.7 ± 8.0	83.7 ± 8.4	101.5 ± 10.4	107.0 ± 9.2
WC ≥102 cm (men)/≥88 cm (women) (%, (n))	2.5 (12)	3.8 (13)	89.9 (143)	95.8 (568)
Systolic blood pressure (mmHg)	116.3 ± 16.2	136.5 ± 19.5	124.7 ± 16.3	138.2 ± 19.4
Diastolic blood pressure (mmHg)	73.5 ± 8.4	83.0 ± 9.6	78.9 ± 9.0	84.3 ± 10.4
Antihypertensive medication (yes) (%, (n))	9.5 (46)	34.6 (120)	20.8 (33)	54.5 (323)
HDL cholesterol (mg/dl)	70.9 ± 15.7	60.7 ± 18.2	62.2 ± 13.7	50.6 ± 13.7
Triglycerides (mg/dl)	84 (66; 110)	135 (92; 184)	106 (85; 130)	164 (122; 220)
Intake of fibrates or nicotinic acids (yes) (%, (n))	0	1.4 (5)	0	2.7 (16)
Intake of statins (yes) (%, (n))	5.8 (28)	10.7 (37)	5.0 (8)	11.3 (67)
Type-2 Diabetes (yes) (%, (n))	1.4 (7)	12.4 (43)	3.8 (6)	26.8 (159)
Fasting blood glucose	97.3 ± 9.6	111.0 ± 23.8	100.2 ± 12.1	117.9 ± 26.3
HbA1c [%]	5.2 ± 0.5	5.4 ± 0.8	5.3 ± 0.5	5.8 ± 0.9
School education (%, (n))				
Low	42.8 (208)	55.6 (193)	62.9 (100)	72.1 (427)
Medium	25.9 (126)	19.3 (67)	16.4 (26)	14.3 (85)
High	31.3 (152)	25.1 (87)	20.8 (33)	13.7 (81)
Smoking (%, (n))				
Current	24.5 (119)	35.5 (123)	16.4 (26)	15.5 (92)
Former	28.2 (137)	26.5 (92)	27.7 (44)	38.8 (230)
Never	47.3 (230)	38.0 (132)	56.0 (89)	45.7 (271)
Metabolic equivalents/week	32.8 (17.0; 54.3)	30.7 (13.3; 58.5)	27.2 (11.5; 49.2)	30.0 (13.3; 55.5)
CAC > 0 (%, (n))	40.3 (196)	65.4 (227)	67.3 (107)	81.8 (485)
CAC at baseline (Agatston units)	0 (0; 15.0)	16.5 (0; 135.6)	4.1 (0; 48.7)	32.5 (2.6; 163.7)

Values are expressed as mean ± standard deviation, median (first quartile, third quartile), or proportion (%).
CAC: coronary artery calcification.
[a] Based on MHO definition 1 (≤1 NCEP ATP III criteria fulfilled).
[b] For a corresponding table based on MHO definition 2, cf. supplementary Table 2.

CAC was more prevalent in persons with MHO than in persons with MHNW (prevalence ratio (PR) = 1.59 (95% CI: 1.38–1.84) for the 1st, 1.70 (1.22–2.36) for the 2nd, 1.68 (1.43–1.97) for the 3rd, and 1.45 (1.27–1.65) for the 4th definition) (Table 2). Prevalence ratios for MUO and MUNW are in the same order of magnitude as the prevalence ratios for MHO.

Results from ordinal logistic regression analyses show that persons with MHO had a slightly higher chance than persons with MHNW to undergo stronger CAC progression according to the three categories of annual CAC change (ORs ranged from 1.24 (0.78–1.97), to 1.48 (1.02–2.13) when the four MHO definitions were used) (Table 3, model 2). However, the corresponding ORs ranged between 2.08 and 2.80 when persons with MUO and MUNW were compared to persons with MHNW (Table 3, model 2).

The odds of CAC progression faster than extrapolated from baseline CAC values was slightly larger in MHO than in MHNW persons (odds ratios ranged from 1.17 (0.69–1.99) to 1.29 (0.87–1.91)) (Table 4, model 2).

The proportions of persons who were metabolically healthy at baseline but no more at 5-year follow-up were 52.6% for MHO, and 28.7% for MHNW when the 1st definition of MHO was used. For metabolically unhealthy persons, the proportions of persons returning to metabolic health were 9.5% for MUO, and 22.1% for MUNW. In adjusted modified Poisson regression analysis with robust variance, the risk of conversion to a metabolically unhealthy status was 1.69 (95% CI: 1.37–2.09) times larger in MHO than in MHNW.

Supplementary Table 3 shows sex-stratified results. We calculated p-values for interaction terms of sex and presence of MHO phenotype which were 0.80 for the prevalence ratio for prevalence of CAC at baseline, 0.85 for the odds ratio for CAC progression faster than expected, and 0.26 for the odds ratio for annual CAC change. These p-values give little evidence for heterogeneous effects in men and women.

Discussion

In our study, prevalence of CAC was larger in persons with MHO than in persons with MHNW. In analyses with

Table 2 Prevalence ratios (95% confidence interval) for the associations between presence of coronary artery calcification and groups of metabolic health and obesity: the Heinz Nixdorf Recall Study.

	N	Presence of CAC at baseline (n (%))	PR (95% CI)	
			Model 1	Model 2
1st MHO definition[a]				
MHO	159	107 (67.3)	1.67 (1.43–1.94)	1.59 (1.38–1.84)
MUO	593	485 (81.8)	2.02 (1.81–2.27)	1.72 (1.54–1.93)
MUNW	347	227 (65.4)	1.62 (1.42–1.85)	1.40 (1.23–1.59)
MHNW (ref)	486	196 (40.3)	1	1
2nd MHO definition[b]				
MHO	31	19 (61.3)	1.78 (1.26–2.51)	1.70 (1.22–2.36)
MUO	721	573 (79.5)	2.31 (1.88–2.83)	1.85 (1.52–2.25)
MUNW	650	360 (55.4)	1.61 (1.30–1.99)	1.35 (1.10–1.66)
MHNW (ref)	183	63 (34.4)	1	1
3rd MHO definition[c]				
MHO	107	75 (70.1)	1.82 (1.53–2.16)	1.68 (1.43–1.97)
MUO	642	515 (80.2)	2.08 (1.84–2.36)	1.78 (1.57–2.01)
MUNW	388	251 (64.7)	1.68 (1.46–1.93)	1.44 (1.26–1.65)
MHNW (ref)	444	171 (38.5)	1	1
4th MHO definition[d]				
MHO	325	198 (60.9)	1.51 (1.32–1.74)	1.45 (1.27–1.65)
MUO	945	736 (77.9)	1.93 (1.73–2.16)	1.68 (1.50–1.88)
MUNW	366	250 (68.3)	1.70 (1.49–1.93)	1.45 (1.28–1.64)
MHNW (ref)	489	197 (40.3)	1	1

MHO: metabolically healthy obesity; MUO: metabolically unhealthy obesity; MUNW: metabolically unhealthy normal weight; MHNW: metabolically healthy normal weight; CAC: coronary artery calcification; PR: prevalence ratio; CI: confidence interval.
Model 1: crude model.
Model 2: adjusted for age, sex, smoking (current, former, never), physical activity, education.
[a] Obesity defined by BMI $\geq$30 kg/m^2; metabolic health defined by $\leq$1 of the following abnormalities: hypertension; decreased HDL cholesterol level; elevated triglycerides level; elevated glucose level.
[b] Like definition 1, but metabolic health defined by 0 abnormality.
[c] Like definition 1, but hsCRP $\geq$0.3 mg/dl included as an additional metabolic abnormality.
[d] Like definition 1, but obesity defined by waist circumference $\geq$102 cm in men/$\geq$88 cm in women.

annual CAC change, persons with MHO showed slightly stronger CAC progression than persons with MHNW, but less strong CAC progression than metabolically unhealthy persons. Furthermore, we found that persons with MHO have a larger risk of converting to a metabolically unhealthy status than persons with MHNW.

We fitted eight models with CAC progression as the outcome (four MHO definitions times two statistical approaches). In these longitudinal analyses, the odds ratios for the comparison of MHO with MHNW ranged from 1.17 (95% CI: 0.69–1.99) to 1.48 (1.02–2.13). Although these confidence intervals were rather wide, all odds ratios were above 1, and from the consistency of these estimates, we conclude that the chance of CAC progression is larger in MHO than in MHNW.

So far, very few studies on MHO CAC associations have been carried out, all but one in Asian populations, and most but not all of these cross-sectional and longitudinal studies showed larger CAC prevalence and stronger CAC progression in MHO persons as compared to their normal weight counterparts [11–17]. Moreover, there are few studies on the association between MHO and other measures of subclinical atherosclerosis which emphasize the evidence that MHO is associated with clinical atherosclerosis [24,25]. Kim et al. defined obesity by BMI $\geq$25 kg/m^2, and used abnormal carotid intima-media thickness and carotid plaque as markers of subclinical carotid atherosclerosis. In their longitudinal study, the adjusted hazard ratio for the development of incident subclinical atherosclerosis was 1.54 (95% CI: 1.38–1.72) for the comparison of MHO to MNHW [25]. Thus, our results are in agreement with (mainly Asian) studies on the association between MHO and subclinical atherosclerosis. In a recent meta-analysis on metabolic health obesity and CVD, the relative risk increase was 45%, 131% and 107% in MHO, MUO and MUNW, respectively, compared with MHNW [7]. This is in line with our results on MHO (with WC-defined obesity) and annual CAC change showing corresponding odds ratios of 1.48, 2.36, and 2.09. Thus, from longitudinal analyses, MHO may be a better condition than MUO and MUNW, but less favorable than MHNW.

Definition of MHO

So far, there is no consensus on a definition of MHO, and there is an enormous variety of definitions used in studies [4]. MHO definitions differ in the definition of obesity, the selection of criteria, and the number of abnormalities defining metabolic disorder:

In most studies, BMI $\geq$30 kg/m^2 is used to define obesity. However, in the above mentioned studies on MHO CAC associations which were mainly done in Asian populations BMI $\geq$25 kg/m^2 was used as obesity cut-off. This accords with recommendations of the World Health Organization Western Pacific Region which suggested

Table 3 Odds ratios (95% confidence interval) for the association between groups of metabolic health and obesity and annual CAC change calculated from ordinal logistic regression models: the Heinz Nixdorf Recall Study.

	N	Change of CAC between 1st and 2nd visit to the study center (%, (n))			OR (95% CI)	
		<10 AU	10–99 AU	≥100 AU	Model 1	Model 2
1st MHO definition[a]						
MHO	159	77.4 (123)	20.1 (32)	2.5 (4)	1.38 (0.89–2.14)	1.24 (0.78–1.97)
MUO	593	56.5 (335)	34.7 (206)	8.8 (52)	3.72 (2.81–4.94)	2.41 (1.76–3.29)
MUNW	347	60.8 (211)	33.1 (115)	6.1 (21)	3.04 (2.21–4.17)	2.08 (1.49–2.91)
MHNW (ref)	486	82.5 (401)	15.8 (77)	1.7 (8)	1	1
2nd MHO definition[b]						
MHO	31	83.9 (26)	16.1 (5)	0 (0)	1.45 (0.50–4.21)	1.29 (0.43–3.90)
MUO	721	59.9 (432)	32.3 (233)	7.8 (56)	5.24 (3.25–8.45)	2.80 (1.69–4.64)
MUNW	650	69.2 (450)	26.6 (173)	4.2 (27)	3.41 (2.10–5.53)	2.08 (1.26–3.43)
MHNW (ref)	183	88.5 (162)	10.4 (19)	1.1 (2)	1	1
3rd MHO definition[c]						
MHO	107	74.8 (80)	22.4 (24)	2.8 (3)	1.78 (1.08–2.95)	1.41 (0.82–2.41)
MUO	642	58.7 (377)	33.2 (213)	8.1 (52)	3.80 (2.82–5.12)	2.48 (1.79–3.44)
MUNW	388	61.3 (238)	32.2 (125)	6.4 (25)	3.36 (2.43–4.64)	2.27 (1.61–3.21)
MHNW (ref)	444	84.0 (373)	15.1 (67)	0.9 (4)	1	1
4th MHO definition[d]						
MHO	325	74.5 (242)	23.4 (76)	2.2 (7)	1.65 (1.17–2.32)	1.48 (1.02–2.13)
MUO	945	59.4 (561)	33.7 (318)	7.0 (66)	3.37 (2.58–4.41)	2.36 (1.76–3.15)
MUNW	366	60.1 (220)	33.9 (124)	6.0 (22)	3.23 (2.36–4.41)	2.09 (1.50–2.92)
MHNW (ref)	489	82.8 (405)	16.0 (78)	1.2 (6)	1	1

MHO: metabolically healthy obesity; MUO: metabolically unhealthy obesity; MUNW: metabolically unhealthy normal weight; MHNW: metabolically healthy normal weight; AU: Agatston units; CAC: coronary artery calcification; OR: odds ratio; CI: confidence interval.
Model 1: crude model.
Model 2: adjusted for age, sex, smoking (current, former, never), physical activity, education.
[a] Obesity defined by BMI ≥30 kg/m^2; metabolic health defined by ≤1 of the following abnormalities: hypertension; decreased HDL cholesterol level; elevated triglycerides level; elevated glucose level.
[b] Like definition 1, but metabolic health defined by 0 abnormality.
[c] Like definition 1, but hsCRP ≥0.3 mg/dl included as an additional metabolic abnormality.
[d] Like definition 1, but obesity defined by waist circumference ≥102 cm in men/≥88 cm in women.

lower cut-offs for Asian populations [26]. When we used waist circumference instead of BMI to define obesity, results were largely the same – with annual CAC change as the outcome in the longitudinal analysis, the association between MHO and CAC change was stronger than in the corresponding analyses with BMI-defined obesity.

According to the review by Rey-López [4], in more than 70% of population-based studies, blood pressure, lipids and fasting plasma glucose were used to define MHO; in 30–40% of the studies, HOMA-IR, WC and diabetes were used; other criteria like C-reactive protein (CRP) or total cholesterol were less often used. As a matter of consequence, reported prevalence of MHO varies widely depending on the definition used. In 27 population-based studies, a range between 6 and 75% was found for MHO prevalence [4]. Generally, MHO prevalence is largest when – as done by many authors – metabolic health is defined by the mere absence of the metabolic syndrome as defined by the NCEP ATP III or International Diabetes Federation (IDF). In our older population, MHO prevalence was 4.1% (metabolic health: no NCEP ATP III criterion fulfilled) and 25.6% (WC-defined obesity, metabolic health: ≤1 NCEP ATP III criterion fulfilled). Surprisingly, in our analyses, lowering the number of fulfilled NCEP ATP III criteria in the definition of metabolic health from ≤1 to 0 did not have a strong influence on our results.

Is MHO a benign condition?

In our study, persons with MHO showed a more adverse metabolic profile than persons with MHNW. This observation had also been made by other authors and may be a first hint that MHO is not a mere benign condition [13]. Our results, especially from cross-sectional analyses, suggested that subclinical atherosclerosis as measured by CAC is more adverse in persons with MHO than in persons with MHNW. Furthermore, in our study, the state of metabolic health was less stable in persons with MHO than in persons with MHNW, and the first were much more likely to fulfill the criteria of the metabolic syndrome at 5-year follow-up than the latter. This is in line with earlier studies showing that a large proportion of persons with MHO convert to MUO [27,28].

Thus, our results confirm that MHO is not a benign condition. This was also found by studies on MHO CVD and MHO diabetes associations [6,7,29]. As an example, in a meta-analysis Bell et al. found a 4.0 (95% CI: 2.7–6.1) fold higher risk of type 2 diabetes in persons with MHO compared to persons with MHNW [29]. Finally, apart from metabolic risks, obesity also has mechanical impacts leading to sleep apnea, reflux disease or knee osteoarthritis [30].

Our result that obesity is not benign with regard to atherosclerosis even in metabolically healthy persons is

Table 4 Odds ratios (95% confidence interval) for the association between groups of metabolic health and obesity and rapid CAC progression calculated from multinomial logistic regression models: the Heinz Nixdorf Recall Study.

	N	n (%) (as expected) (reference)[e]	n (%) (faster than expected)[e]	OR (95% CI)	
				Model 1	Model 2
1st MHO definition[a]					
MHO	159	93 (58.5)	22 (13.8)	1.02 (0.60–1.72)	1.17 (0.69–1.99)
MUO	593	378 (63.7)	115 (19.4)	1.31 (0.95–1.80)	1.55 (1.09–2.19)
MUNW	347	249 (71.8)	80 (23.1)	1.38 (0.98–1.96)	1.38 (0.96–1.98)
MHNW (ref)	486	357 (73.5)	83 (17.1)	1	1
2nd MHO definition[b]					
MHO	31	19 (61.3)	6 (19.4)	1.24 (0.46–3.33)	1.29 (0.47–3.54)
MUO	721	452 (62.7)	131 (18.2)	1.13 (0.74–1.73)	1.34 (0.85–2.11)
MUNW	650	473 (72.8)	129 (19.9)	1.07 (0.70–1.63)	1.08 (0.70–1.67)
MHNW (ref)	183	133 (72.7)	34 (18.6)	1	1
3rd MHO definition[c]					
MHO	107	62 (57.9)	16 (15.0)	1.12 (0.61–2.05)	1.28 (0.69–2.37)
MUO	642	407 (63.4)	120 (18.7)	1.28 (0.93–1.77)	1.51 (1.06–2.16)
MUNW	388	280 (72.2)	88 (22.7)	1.36 (0.96–1.93)	1.37 (0.95–1.96)
MHNW (ref)	444	325 (73.2)	75 (16.9)	1	1
4th MHO definition[d]					
MHO	325	208 (64.0)	55 (16.9)	1.08 (0.74–1.58)	1.29 (0.87–1.91)
MUO	945	612 (64.8)	188 (19.9)	1.25 (0.94–1.67)	1.59 (1.17–2.16)
MUNW	366	276 (75.4)	76 (20.8)	1.12 (0.80–1.59)	1.19 (0.83–1.71)
MHNW (ref)	489	351 (71.8)	86 (17.6)	1	1

MHO: metabolically healthy obesity; MUO: metabolically unhealthy obesity; MUNW: metabolically unhealthy normal weight; MHNW: metabolically healthy normal weight; CAC: coronary artery calcification; OR: odds ratio; CI: confidence interval.
Model 1: crude model.
Model 2: adjusted for age, sex, smoking (current, former, never), physical activity, education.
[a] Obesity defined by BMI $\geq$30 kg/m^2; metabolic health defined by $\leq$1 of the following abnormalities: hypertension; decreased HDL cholesterol level; elevated triglycerides level; elevated glucose level.
[b] Like definition 1, but metabolic health defined by 0 abnormality.
[c] Like definition 1, but hsCRP $\geq$0.3 mg/dl included as an additional metabolic abnormality.
[d] Like definition 1, but obesity defined by waist circumference $\geq$102 cm in men/$\geq$88 cm in women.
[e] “As expected” refers to an extrapolation of baseline CAC values (cf. methods section).

also in line with recent findings from the UK biobank [31]. This study demonstrated for five different anthropometric measures that overweight and obesity increased cardiovascular risk, and these associations were stronger for measures of abdominal adiposity than for BMI. However, weight reduction targets recommended by guidelines are often not met, and from the EUROASPIRE (European Action on Secondary Prevention through Intervention to Reduce Events) surveys it became apparent that even coronary patients often fail to manage obesity [32,33].

Strengths and limitations

Some limitations have to be considered. First, the number of persons with MHO was small for our MHO definitions, and confidence intervals were rather wide in longitudinal analyses. However, this indicates that MHO is a rather rare phenomenon, in particular when MHO is defined by a complete lack of metabolic abnormalities. Second, our study lacks assessment of non-alcoholic fatty liver disease, which is a strong risk factor for clinically relevant cardiovascular events.

Strengths of our study are its population-based design and the highly standardized measurement of cardiovascular risk factors. Moreover, it is the first study on MHO CAC associations in Caucasians which does not only include cross-sectional but also longitudinal analyses. CAC was carefully assessed by EBCT at two points in time with a 5-year follow-up. Furthermore, we did not only use the original NCEP ATP III definition for metabolic health but we also used three other MHO definitions (a stricter MHO definition where none of the NCEP ATP III criteria was tolerated; one which included hsCRP; one with WC-based obesity).

Conclusions

Our analyses of MHO CAC associations add to the evidence that MHO is not a benign condition. For four definitions of MHO, CAC was more prevalent in persons with MHO than in persons with MHNW. Longitudinal analyses with annual CAC change as the outcome indicated that MHO may be a better condition than MUO and MUNW, but less favorable than MHNW.

Conflicts of interest

None declared.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.numecd.2018.11.002.

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