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Healthy overweight and obesity in the young: Prevalence and risk of major adverse cardiovascular events

Paolo Palatini [a,*], Francesca Saladini [b], Lucio Mos [c], Olga Vriz [c], Andrea Ermolao [a], Francesca Battista [a], Giuseppe Berton [d], Mattia Canevari [c], Marcello Rattazzi [a]

[a] *Department of Medicine - University of Padova, Padova, Italy*
[b] *Cittadella Town Hospital, Cittadella, Italy*
[c] *San Antonio Hospital, San Daniele del Friuli, Italy*
[d] *The ABC Heart Disease Foundation-ONLUS, Conegliano, Italy*

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Abstract *Aims:* To investigate the prevalence of metabolically healthy overweight/obesity and to study its longitudinal association with major adverse cardiovascular and renal events (MARCE).
Methods and results: The study was conducted in 1210 young-to-middle-age subjects grouped according to their BMI and metabolic status. The risk of MARCE was evaluated during 17.4 years of follow-up. Forty-eight-percent of the participants had normal weight, 41.9% had overweight, and 9.3% had obesity. Metabolically healthy status was found in 31.1% of subjects with normal weight and in 20.0% of those with overweight/obesity. During the follow-up, there were 108 MARCE. In multivariate Cox analysis adjusted for confounders and risk factors, no association was found between MARCE and overweight/obesity ($p = 0.49$). In contrast, metabolic status considered as a two-class variable (0 versus at least one metabolic abnormality) was a significant predictor of MARCE (HR, 2.11; 95%CI, 1.21–3.70, $p = 0.009$). Exclusion of atrial fibrillation from MARCE ($N = 87$) provided similar results (HR, 2.11; 95%CI, 1.07–4.16, $p = 0.030$). Inclusion of average 24 h BP in the regression model attenuated the strength of the associations. Compared to the group with healthy metabolic status, the metabolically unhealthy overweight/obesity participants had an increased risk of MARCE with an adjusted HR of 2.33 (95%CI, 1.05–5.19, $p = 0.038$). Among the metabolically healthy individuals, the CV risk did not differ according to BMI group ($p = 0.53$).
Conclusion: The present data show that the risk of MARCE is not increased in young metabolically healthy overweight/obesity suggesting that the clinical approach to people with high BMI should focus on parameters of metabolic health rather than on BMI.

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* Corresponding author. Studium Patavinum and Department of Medicine – University of Padova, 35128 Padua, Italy.
E-mail address: palatini@unipd.it (P. Palatini).

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1. Introduction

Epidemiologic evidence indicates that high body mass index (BMI) is an independent risk factor for cardiovascular (CV) events and mortality [1,2]. However, meta-analyses have shown that the evidence regarding the longitudinal association between BMI and hard end points is inconsistent, especially with regards to overweight and class I obese individuals (Ov-Ob), with some studies showing increased risk of adverse outcomes in Ov-Ob and others demonstrating similar or even lower risk than in normal weight individuals [3–9]. These inconsistent results may be due to the different metabolic characteristics of the participants across the various studies. Indeed, a number of studies have shown that the risk of adverse CV outcomes associated with Ov-Ob greatly varies depending on the underlying metabolic condition, being lower in people who exhibit a better metabolic profile [3–9]. Among these, a unique subset of obese individuals without overt cardiometabolic abnormalities has been identified, a condition defined metabolically healthy obesity (MHO) [3,4,6,8]. However, the impact of MHO on CV disease is still controversial, as some findings indicate that subjects with MHO do not have a higher CV risk than normal weight individuals, while some others suggest that they have an increased risk although lower than that of metabolically unhealthy obese counterparts. Part of this controversy may be due to the inconsistent definition of metabolic health, the inclusion of overweight subjects in the MHO groups, and to the different age of the study participants [3].

Some studies suggest that MHO is less common in elderly subjects than in younger obese individuals [10]. In addition, in the old age there is often a U-shaped relationship between BMI and CV risk, which may obscure the prognostic role of obesity either associated or not with unhealthy metabolic status [11].

During the last 4 decades, the prevalence of obesity among young individuals has steadily increased and more than half of young adults currently meet the criteria for Ov-Ob [12]. This emphasizes the importance of delivering effective and cost-efficient interventions in this age range identifying the individuals who are at heightened CV risk. However, only limited prognostic data do exist in young to middle age people who will be exposed to the possible deleterious effects of Ov-Ob all along the life course.

Thus, in the present study we investigated the risk of major CV and renal events (MARCE) associated with ObOv in the participants of the Hypertension and Ambulatory Recording VEnetia STudy (HARVEST) [13–15]. The main purpose was to quantify the risk of MARCE according to metabolic status in the subjects stratified by BMI category.

2. Methods

2.1. Population

Study participants were 1210 subjects from the HARVEST, a multicentre observational study, performed in North East Italy [13–15]. Participants were selected by the local general practitioners who had been contacted by letter, phone call and local meetings, according to the following clinical characteristics: age between 18 and 45 years, systolic blood pressure (BP) of 140–159 mmHg and/or a diastolic BP of 90–99 mmHg, no antihypertensive therapy or any other treatment for cardiovascular diseases, absence of diabetes mellitus, previous CV events, renal impairment, and other serious illnesses. Eligible subjects were then sent to one of the 17 hypertension units that agreed to participate in the study. More information regarding inclusion and exclusion criteria were previously published [13–17]. The present analysis was conducted in the participants who had office and ambulatory BP and heart rate, BMI, and metabolic data at baseline. The study was initiated on April 1st, 1990 and was approved by the HARVEST Ethics Committee and was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments. A written informed consent was given by all study participants.

2.2. Procedures

Clinical information on medical history, family history of CV disease and lifestyle habits was collected by means of a self-reported questionnaire [16]. Smoking, physical activity, alcohol drinking, and coffee consumption were taken into account in agreement with previous HARVEST studies [16] and were classified according to previously published procedures (see supplementary material). At baseline, participants underwent physical examination, anthropometry, and blood chemistry after an overnight fast. Office BP was measured in triplicate in the lying and standing positions with the auscultatory method using a mercury sphygmomanometer provided with a cuff of appropriate dimensions. Then the participant was scheduled for ambulatory BP monitoring which was performed with the A&D TM2420 model 7 (A&D, Tokyo, Japan) or ICR Spacelabs 90,207 monitor (Spacelabs, Redmond, Washington, USA) devices. Both devices were previously validated and were shown to provide comparable results [18,19]. Before starting the study all investigators underwent common training procedures on the use of the recorders to ensure methodological homogeneity. The device was always applied and taken away in the hospital, using a cuff of the same size as that used to measure office BP. Standard (12 × 24 cm) bladders were used in subjects with arm circumference less than 33 cm and large (15 × 30 cm) bladders in those with arm circumference of 33 cm or greater (maximum circumference = 38 cm). Before the recording was started, the device was checked against a mercury sphygmomanometer by means of a Y tube. Six subsequent BP readings provided by the monitor, three with the subjects in the supine and three in the upright posture, had to agree closely with simultaneous measurements performed by the investigator. When the device was in operation, subjects were requested to keep their arm still and to remain motionless. Ambulatory BP was measured every 10 min during the day (0600–2300 h) and every 15–30 min during the night (2300–0600 h). Participants were instructed

to go to bed and to wake up according to our scheduled times. Patient's adherence was checked from the diary card. All ABPMs were sent to the Coordinating Office in Padova where they were screened for editing of artifactual values based on previously described criteria [13]. Only recordings containing error measurements of 20% or less were considered acceptable for evaluation. The white-coat effect was calculated as the difference between office and average 24-h SBP.

2.3. Follow up

Patients were followed at six-month intervals throughout the observation period. Office BP and lifestyle habits were assessed at each visit. If participants met the criteria for treatment adopted by international guidelines at the time of patients' evaluation (see supplementary material) they were started on antihypertensive therapy. Survival time for the participants was defined as the period from the date of the first visit of the participant to the date of first MARCE.

2.4. Definition of MARCE

Vital status and the incidence of MARCE was ascertained from medical records and interviews with attending physicians and patient's families. The definition of MARCE included all major complications of hypertension as individual outcomes including heart failure, renal events, and peripheral vascular disease. Renal events were defined as a chronic kidney disease stage 3 or higher (estimated glomerular filtration rate <60 ml/min/1.73 m^2). Atrial fibrillation was also taken into account because it is a major risk factor for stroke. However, as atrial fibrillation is not currently considered as a major cardiac event, Cox regressions were repeated after excluding this outcome. Thus, MARCE included fatal and nonfatal strokes, fatal and nonfatal acute myocardial infarction, non ST-elevation acute coronary syndromes, any myocardial revascularization procedure, heart failure needing at least hospitalization, any aortic or lower limb revascularization procedure, development of permanent atrial fibrillation, and chronic kidney disease.

2.5. Definition of ObOv and of metabolic status

Normal body weight was defined as a BMI <25 kg/m^2, overweight as a BMI from 25 to 29.9 kg/m^2 and obesity as a BMI kg/m^2 or higher. In the survival analyses overweight and obesity were lumped together into a single OvOb group. Healthy metabolic status was defined as the absence of any metabolic abnormality in the presence of normal average 24 h BP. Inclusion of ambulatory BP instead of office BP in the definition allowed a more reliable identification of the subjects with normal BP. Thus, healthy metabolic status was defined as having triglyceride levels <150 mg/dL, high-density lipoprotein cholesterol (HDL-cholesterol) ≥ 40 mg/dL in men and ≥ 50 mg/dL in women, fasting glucose <100 mg/dL, and normal average 24 h BP according to the European Society of hypertension cutoff (130/80 mmHg) [20]. Unhealthy metabolic status was defined as a 2-class parameter (absence versus at least one abnormal parameter) or as a 3-class parameter, class 0 versus one abnormal parameter (class 1) or more than one abnormal parameters (class 2).

2.6. Statistics

Quantitative variables were reported as mean and SD, or as median and interquartile range (IQR), and differences in the distribution across groups were tested by ANCOVA test adjusting for age and sex. Categorical variables were reported as percentage and differences in the distribution were tested by χ^2 test. The risk of development of MARCE related to the BMI/metabolic status category was evaluated by means of multivariable Cox proportional hazards analyses, adjusting for age, sex, parental history of CV disease, smoking, alcohol drinking, coffee use, physical activity habits, 24 h heart rate, serum creatinine, and total cholesterol. No violations to the proportional hazards assumption were detected by inspection of survival curves. Hazard ratios and corresponding two-sided 95% confidence intervals were derived from the regression coefficients in the Cox models. A 2-tailed probability value < 0.05 was considered significant. All analyses were performed using Systat version 12 (SPAA Inc., Evanston, IL, U.S.A.) and Medcalc version 15.8 (MedCalc Software, Ostend, Belgium).

3. Results

Mean BMI in the whole sample was 25.1 ± 3.4 kg/m^2. BMI distribution according to metabolic status is shown in supplementary Figure S1. Both distributions were non normal ($p < 0.001$) with a positive coefficient of skewness (0.60, $p < 0.001$). However, in the metabolically healthy subjects the coefficient of Kurtosis was lower (0.32, $p = 0.25$) than in their metabolically unhealthy counterparts (0.75, $p < 0.001$). Forty-eight point eight percent of the participants had normal weight, 41.9% had overweight, and 9.3% had obesity. Among the obese subjects, in only four individuals was BMI higher than 35 kg/m^2.

The characteristics of the HARVEST participants stratified by BMI category are reported in Tables 1 and 2. Compared with normal weight subjects, ObOv participants were slightly older, were more frequently male, had higher office and 24-h DBP and had a worse lifestyle profile. In particular, alcohol use was more frequent among the overweight subjects and sedentariness among the obese participants. The SBP white-coat effect was greater in the obese participants than the other two groups ($p = 0.002$). The metabolic profile progressively impaired on going from the normal weight to the obese individuals. The distribution of the study participants stratified by BMI status and the number of abnormal metabolic parameters is presented in Fig. 1. Among the subjects with normal weight, 31.1% were metabolically healthy (no abnormal parameter), whereas among those with overweight/obesity 20.0% had no abnormal metabolic parameter

Table 1 Characteristics of 1210 HARVEST participants grouped according to body mass index category.

Variable	BMI CATEGORY						p-value
	Normal weight (N = 591)		Overweight (N = 507)		Obese (N = 112)		
	Mean	SD	Mean	SD	Mean	SD	
Age, years	31.5	8.6	34.5	8.16	34.9	8.3	<0.001
BMI, Kg/m^2	22.8	1.7	27.0	1.3	32.3	1.9	<0.001
Office SBP, mmHg	145.3	10.7	145.4	10.4	147.0	10.2	0.27
Office DBP, mmHg	92.7	5.7	94.1	5.7	95.4	5.5	<0.001
Heart rate, bpm	74.8	10.0	74.2	9.1	75.0	8.5	0.53
24-h SBP, mmHg	130.9	11.2	131.9	10.5	128.6	10.7	0.028
24-h DBP, mmHg	80.7	8.8	82.2	7.4	83.4	7.4	0.025
24-h heart rate, bpm	73.1	8.4	72.5	7.8	73.6	8.3	0.29
SBP WCE, mmHg	14.3	13.3	13.5	12.3	18.4	13.2	0.002
Glucose, mg/dL	91.1	11.4	94.7	11.7	96.4	13.1	0.002
TG, mg/dL	94.8	49.3	122.8	69.4	161.3	123.5	<0.001*
HDL-chol, mg/dL	56.1	12.9	49.5	11.8	47.4	12.4	<0.001
Total chol, mg/dL	191.4	36.1	202.5	39.5	208.1	37.8	0.002
Creatinine, mg/dL	0.89	0.17	0.94	0.18	0.91	0.19	0.029

BMI indicates body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; 24 h, average 24 h; TG, triglyceride; chol, cholesterol; WCE, white-coat effect calculated as the difference between office and average 24 h systolic blood pressure. *P*-values for ANCOVA adjusted for age and sex. *Kruskal-Wallis test.

Table 2 Sex, lifestyle factors, metabolic status distribution, and rate of MACE in 1210 HARVEST participants grouped according to body mass index category.

Variable	Normal weight (N = 591)	Overweight (N = 507)	Obese (N = 112)	*P*-value
Sex, female	36.4%	17.2%	24.1.0%	<0.001
Smoking, yes	19.8%	22.3%	21.4%	0.60
Alcohol use, yes	41.6%	56.0%	38.4%	<0.001
Heavy coffee use, yes	7.6%	11.8%	13.4%	<0.001
Sedentary, yes	58.1%	61.5%	76.8%	0.001
Metabolic status, healthy	31.1%	20.1%	19.6%	<0.001
MARCE, yes	7.6%	10.3%	9.8%	0.29

MARCE indicates major adverse cardiovascular and renal events.

(Table 2). In both BMI groups, the majority had only one abnormal parameter.

3.1. Survival analysis

During a median follow-up of 17.4 (IQR 8.9–23.0) years, there were 108 fatal and nonfatal MARCE. The most common events were acute coronary syndromes (n = 50) including 12 coronary revascularizations. The incidence of fatal and nonfatal stroke amounted to 13 cases. Other MARCE included 12 cases with other CV events (heart failure requiring hospitalization = 3, aortic aneurism = 3, peripheral vascular disease = 6), 21 cases with atrial fibrillation, and 12 cases with renal events.

3.2. BMI group as predictor of MARCE

In multivariate Cox analysis adjusted for age, gender, parental history of CV disease, smoking, alcohol drinking, coffee use, physical activity habits, 24 h heart rate, serum creatinine, and total cholesterol, no association was found between MARCE and ObOv (HR, 0.87; 95%CI, 0.58–1.30, p = 0.49) or overweight and obesity considered separately (p > 0.47).

3.3. Metabolic status as predictor of MARCE

In a Cox analysis including the same variables as above, unhealthy metabolic status considered as a two-class variable was a significant predictor of MARCE in the population as a whole with a HR of 2.11 (95%CI, 1.21–3.70, p = 0.009). In the OwOb group the HR was 2.64 (95%CI, 1.17–5.91, p = 0.019) and in the normal weight group it was 1.68 (95%CI, 0.76–3.72, p = 0.20).

When metabolic status was considered as a three-class variable ((absence (reference), one (class 1), or more than one (class 2) metabolic abnormalities)), the HRs were 2.06 (95%CI, 1.14–3.70, p = 0.016) for class 1 and 2.20 (95%CI, 1.19–4.08, p = 0.011) for class 2 unhealthy status.

Exclusion of atrial fibrillation from MARCE (N = 87) provided similar results (HR, 2.11; 95%CI, 1.07–4.16, p = 0.030 for class 1 and 2.32; 95%CI, 1.15–4.70, p = 0.019 for class 2. Inclusion of average 24-h BP in the regression model attenuated the strength of the associations which remained significant for both class 1 (HR, 1.93; 95%CI, 1.03–3.62, p = 0.042) and class 2 (HR, 2.04; 95%CI, 1.04–3.99, p = 0.037) unhealthy metabolic status. Similar results were found when baseline office BP instead of ambulatory BP was taken into account (see supplementary

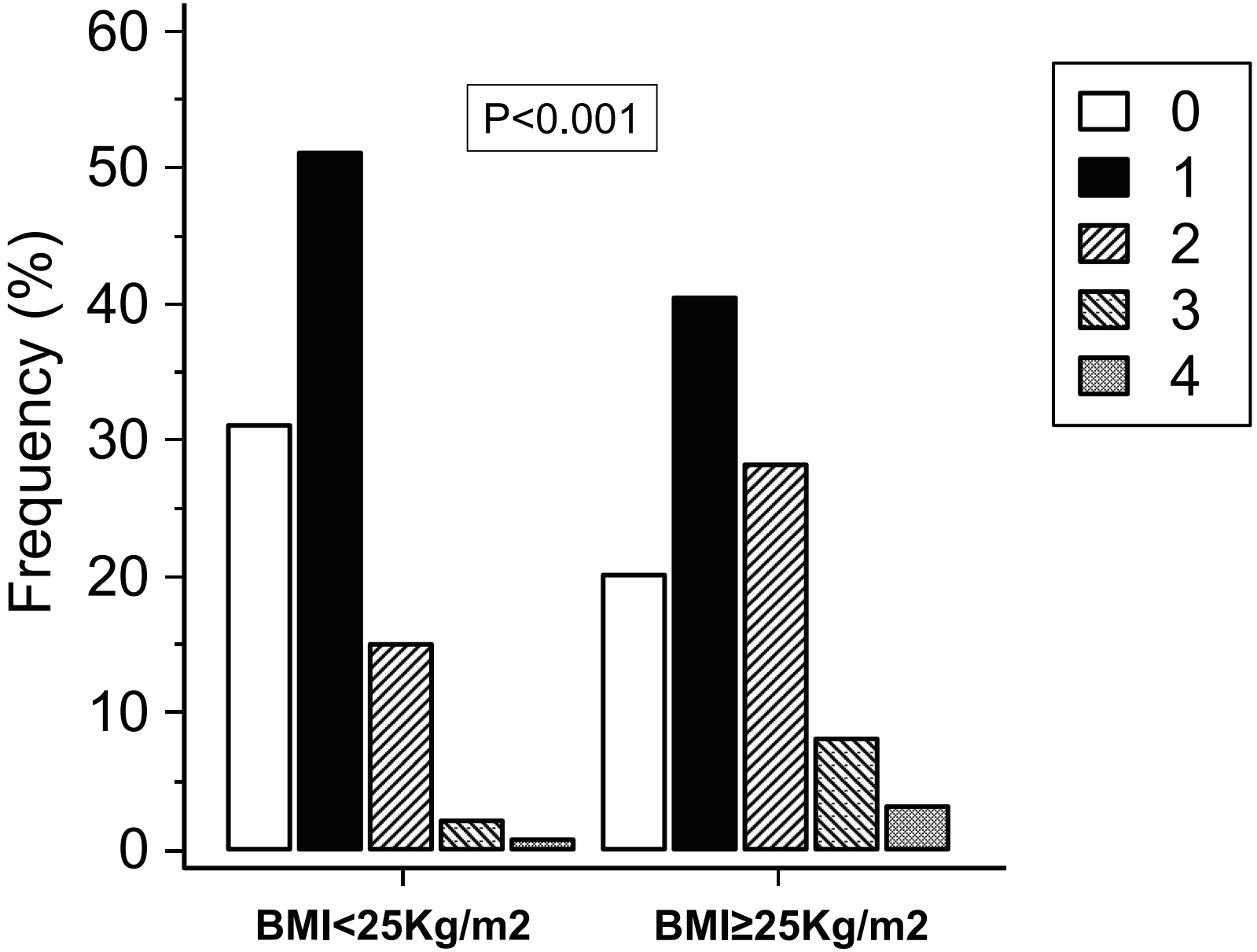

Figure 1 Classification of 1210 HARVEST participants, stratified by BMI status, according to the number of abnormal metabolic parameters. Subjects with one or more abnormal parameters were defined as being metabolically unhealthy.

material). In the OwOb group the association remained significant for class 1 (HR, 2.50 95%CI, 1.03–6.07, p = 0.043) but not for class 2 (HR, 2.27; 95%CI, 0.90–5.71, p = 0.08). Among the participants with normal weight, no significant association with outcome was found for both classes.

3.4. BMI group and metabolic status combined

Participants were further stratified into four categories, 1) normal weight/healthy metabolic status (N = 184), 2) normal weight/unhealthy metabolic status (N = 407), 3) OvOb/healthy metabolic status (N = 124) and 4) OvOb/unhealthy metabolic status (N = 495). Their clinical characteristics are reported in Table 3. High BP was the most frequent abnormal parameter in both metabolically unhealthy groups. The rate of abnormal metabolic parameters was higher in the OvOb participants than in the normal weight subjects. In Fig. 2, the survival curves adjusted for the above covariables are shown. Compared to the group with healthy metabolic status, the metabolically unhealthy OvOb participants had an increased risk of MARCE with an adjusted HR of 2.33 (95%CI, 1.05–5.19, p = 0.038). A greater risk was found also in the normal weight/unhealthy metabolic status group (HR, 2.73; 95%CI, 1.20–6.23, p = 0.017). Among the metabolically healthy individuals, the CV risk did not differ according to BMI group (p = 0.53).

4. Discussion

In this prospective cohort study of young-to-middle-age subjects screened for stage 1 hypertension, we found that metabolically healthy OvOb subjects did not have an increased risk of MARCE compared to the group of normal-weight metabolically healthy participants. In contrast, the risk of MARCE was significantly increased in both metabolically unhealthy groups compared to their metabolically healthy counterparts.

4.1. Prevalence of healthy overweight/obesity

The prevalence of MHO has shown a large variation across different studies due to its inconsistent and often contradictory definition [3–9]. The lack of standardized criteria and cut-off values to define abnormal metabolic parameters represents the major source of variability in the reported MHO prevalence. MHO was defined by most investigators as the presence of obesity in the absence of a clearly defined metabolic disorder, such as insulin resistance, dyslipidemia, hypertension, or diabetes [3–6,8]. Thus in the majority of previous studies MHO subjects had some degree of metabolic abnormalities with high variability in the chosen criteria and threshold values. A meta-analysis of 40 population-based studies concluded that ~35% of all people with obesity in the world are metabolically healthy [9]. However, in recent years a consensus has emerged supporting a stricter definition of MHO which should be considered as the absence of any abnormal metabolic parameters [21,22]. Following this strict definition and considering the largest studies performed in Europe [22] and the United States [21], the prevalence of MHO was reported to range from 12% to 17% of all obese adults. The 20% prevalence found in the

Table 3 Characteristics of 1210 HARVEST participants grouped according to body mass index and metabolic status.

Variable	BMI<25 kg/m^2				BMI≥25 kg/m^2				p-value
	Metab − N = 184		Metab + N = 407		Metab − N = 124		Metab + N = 495		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Age, years	31.4	8.6	31.6	8.6	33.8	7.6	34.8	8.3	<0.001
BMI, Kg/m^2	22.3	1.8	22.9	1.5	27.8	2.5	27.9	2.6	<0.001
Office SBP, mmHg	143.0	10.0	146.2	10.8	142.8	10.1	146.3	10.3	<0.001
Office DBP, mmHg	92.2	5.6	92.9	5.7	93.1	5.7	94.6	5.6	<0.001
Heart rate, bpm	76.0	10.3	74.3	9.8	74.5	9.3	74.2	8.9	0.56
24-h SBP, mmHg	121.6	6.8	135.1	10.1	122.0	5.8	133.7	10.1	<0.001
24-h DBP, mmHg	78.2	8.1	81.8	8.9	79.7	6.6	83.0	7.5	<0.001
Glucose, mg/dL	87.7	7.4	92.6	12.4	89.9	6.5	96.2	12.7	<0.001
TG, mg/dL	79.6	29.6	99.0	58.5	87.2	26.1	142.7	92.9	<0.001*
HDL-chol, mg/dL	60.1	11.5	54.2	13.0	54.1	9.5	47.9	12.1	<0.001
Total chol, mg/dL	193.7	36.6	190.4	35.8	196.3	32.7	205.2	40.6	0.001
Sex, female	48.4%	–	40.0%	–	25.0%	–	16.8%	–	<0.001
Smoking, yes	15.2%	–	21.9%	–	16.1%	–	23.7%	–	0.049
Alcohol use, yes	35.9%	–	44.2%	–	47.6%	–	54.0%	–	<0.001
Coffee drinking, yes	67.9%	–	67.8%	–	79.8%	–	79.5%	–	<0.001
Physically active, no	57.1%	–	58.7%	–	60.5%	–	65.1%	–	0.13
24-h BP +	0%	–	76.9%	–	0%	–	70.6%	–	<0.001
Glucose +	0%	–	24.1%	–	0%	–	37.3%	–	<0.001
TG +	0%	–	16.2%	–	0%	–	28.8%	–	<0.001
HDL-chol +	0%	–	13.5%	–	0%	–	31.4%	–	<0.001

BMI indicates body mass index; Metab -, subjects with no abnormal metabolic parameter; Metab +, subjects with at least one abnormal metabolic parameter; SBP, systolic blood pressure; DBP, diastolic blood pressure; 24 h, average 24 h; TG, triglyceride; chol, cholesterol. + abnormal parameter; *P*-values for ANCOVA adjusted for age and sex. *Kruskal-Wallis test.

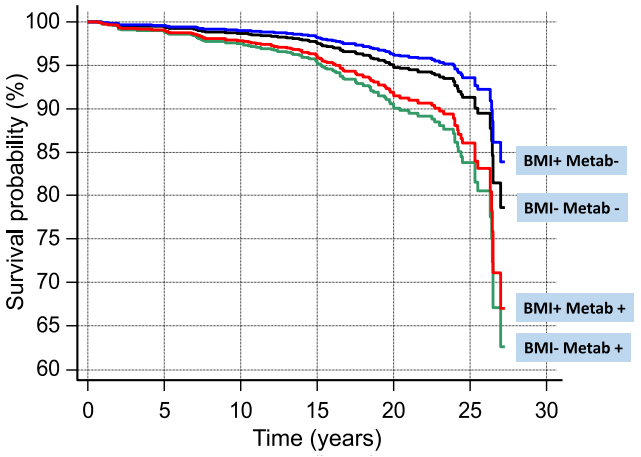

Figure 2 Survival curves for risk of major adverse cardiovascular and renal events in the participants stratified according to body mass index and metabolic status. The risk was calculated from multivariable Cox regressions adjusted for age, sex, parental history of CV disease, smoking, alcohol drinking, coffee use, physical activity habits, 24-h heart rate, serum creatinine, and total cholesterol. BMI- indicates participants with normal body weight; BMI+, participants with overweight/obesity; Metab-, participants with healthy metabolic status; Metab+, participants with unhealthy metabolic status.

present study is in line with that observed in those previous reports and is very close to that of the Italian CHRIS cohorts (19%) [23]. The slightly higher percentage of MHO subjects found in our cohort may be due to the nature of our population. The HARVEST participants are young to middle age individuals, mostly males with mildly elevated BP at enrolment, and only a minority had obesity (with BMI <35 kg/m^2 in almost all subjects). All these characteristics have shown to affect the prevalence of MHO in previous studies [24,25].

4.2. Risk of MARCE

Obesity not only increases the likelihood of developing CV risk factors, such as hypertension or diabetes, but is also an independent risk factor for CV diseases, including atrial fibrillation [26–28]. A recent study demonstrated a 3-fold increase in obesity-related CV mortality rate in the US population from 1999 to 2020 [2].

However, in our young-to-middle-age participants, although the rate of MARCE was slightly increased in the ObOv groups, in a Cox analysis including other risk factors and several confounders no independent association was found between OvOb and adverse outcomes. Some studies have shown that the CV effects of obesity depend not only on excess body weight but also on the duration of obesity [29]. Other studies suggested that the risk of all-cause mortality may increase in relation to the number of years that an individual is obese independently of current BMI [30]. Thus, the young age of our participants is a possible reason for the lack of association of OvOb with MARCE in our study.

The main finding of the present report is that a clear increase in CV risk was present in the subjects with unhealthy metabolic status. As this association might be influenced by the selection criteria used to identify the metabolically unhealthy groups – e.g. the higher ambulatory BP at baseline -, data were adjusted also for baseline 24 h BP. The association remained significant also when ambulatory BP was accounted for in both the population as a whole and the OwOb subgroup indicating that not only high BP but also metabolic abnormalities were responsible for the increased risk of MARCE. The results did not change substantially when office BP was taken into account. According to a recent meta-analysis of 22 studies, people with MHO defined by the absence of metabolic syndrome were at increased risk of CV events compared with healthy normal-weight participants [3]. However, in only 3 out of the 22 prospective studies was MHO defined as the absence of all metabolic abnormalities as we did in the present study [3]. In the pooled analysis of these three studies, the obese participants without any metabolic abnormality had no significant increase in CV risk.

In the present study metabolic data were obtained only at baseline. Prospective studies have revealed that MHO status may be transient in nature and that a considerable proportion of MHO individuals may lose this condition over time [9,31–33]. However, despite a possible transition to the unhealthy condition the group with healthy OvOb at the baseline had the same risk of developing MARCE during the follow-up as the normal weight metabolically healthy group. Whether non resilient MHO status is associated with increased CV risk is still a matter for debate. Some studies which evaluated non-resilient MHO status in relation to future cardiometabolic outcomes found a positive association with CV events [31,33] whereas others failed to find this association [34]. On the other hand, a transition to unhealthy metabolic status can occur also in normal weight subjects.

4.3. Limitations

Some limitations of the present study should be noted. First, waist circumference or waist-hip-ratio which are better indicators of visceral fat accumulation were not available. However, in the NHANES study no difference in the prevalence of MHO was found when waist circumference was used instead of BMI to define the MHO phenotype [21]. Second, in our cohort there was a lower prevalence of females because of the natural selection of people with high BP in this age range [35], which may have decreased the prevalence of MHO. Third, the present results mainly apply to people with overweight because obesity was present in only a minority of our participants. Fourth, the present data were obtained in people screened for stage 1 hypertension and not from a general population and thus high BP played a more important role in the calculation of unhealthy metabolic status. Fifth, changes in BP, body weight and lifestyle, new-onset diabetes mellitus, and beginning of antihypertensive treatment during the follow-up, which may have affected the outcome, were not included in the survival analyses. A strength of our study is that BP was measured with 24-h ambulatory monitoring

thereby increasing the likelihood of including people with normal BP in the metabolically healthy groups.

5. Conclusions

Given the serious health problems associated with overweight and obesity, including CV disease and increased mortality, the identification of people with metabolically healthy phenotype may be helpful for developing appropriate interventions for obese patients. The concept that obesity is always a detrimental clinical condition should be reviewed. The present data show that the risk of future MARCE is not increased in young-to-middle-age metabolically healthy OvOb when the condition is defined according to strict criteria. This suggests that the clinical approach to OvOb should focus on parameters of metabolic health rather than on BMI. Differentiating obese people at low CV risk from those at higher risk will allow healthcare professionals to identify those patients in whom a more aggressive strategy of weight loss should be pursued. It has been shown that even a modest weight loss can convert to MHO up to 30% of metabolically unhealthy obese patients [36,37]. However, absence of metabolic risk factors in people with obesity should not be an indication for labelling these subjects as "healthy". Recent data from five population-based cross-sectional studies have shown that children and adolescents with metabolically healthy overweight or obesity had greater odds of having increased carotid intima-media thickness in comparison with their metabolically healthy normal weight counterparts [38]. In addition, data from the NHANES investigators has shown that a decline in healthy weight has occurred in the USA during the last two decades [39]. Given the instability of MHO, it seems appropriate to advise obese people without metabolic abnormalities to maintain or adopt a healthy lifestyle to avoid the transition to a metabolically unhealthy condition.

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Declaration of competing interest

The authors declare that they have no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2023.11.013.

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