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Transition from metabolically benign to metabolically unhealthy obesity and 10-year cardiovascular disease incidence: The ATTICA cohort study

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ABSTRACT

Background/Objectives: Metabolically benign obesity remains a scientific field of considerable debate. The aim of the present work was to evaluate whether metabolically healthy obese (MHO) status is a transient condition which propagates 10-year cardiovascular disease (CVD) onset.
Methods: A prospective longitudinal study was conducted during 2001–2012, the ATTICA study studying 1514 (49.8%) men and 1528 (50.2%) women (aged >18 years old) free of CVD and residing in the greater Athens area, Greece. Follow-up assessment of first combined CVD event (2011−2012) was achieved in $n = 2020$ participants; of them, 317 (15.7%) incident cases were identified. Obesity was defined as body mass index ≥30 kg/m^2 and healthy metabolic status as absence of all NCEP ATP III (2005) metabolic syndrome components (excluding waist circumference).
Results: The MHO prevalence was 4.8% ($n = 146$) with 28.2% of obese participants presenting metabolically healthy status at baseline. Within this group, 52% developed unhealthy metabolic status during the 10-year follow up. MHO vs. metabolically healthy non-obese participants had a higher likelihood of presenting with 10-year CVD events, yet only the subset of them who lost their baseline status reached the level of significance (Hazard Ratio (HR) = 1.43, 95% Confidence Interval (95% CI) 1.02, 2.01). Sensitivity analyses revealed that MHO status was independently associated with elevated CVD risk in women and participants with low adherence to the Mediterranean diet, low grade inflammation, and insulin resistance.
Conclusions: MHO status is a transient condition where weight management is demanded to prevent the establishment of unhealthy cardiometabolic features. The existence of obese persons who remain "longitudinally" resilient to metabolic abnormalities is an emerging area of future research.

1. Introduction

Metabolically benign obesity remains a scientific field of considerable debate in the primary prevention spectrum of CVD [1]. Most recent meta-analytic findings corroborate that metabolically benign obesity may in fact not be an innocuous low-risk condition as previously believed, underscoring that former literature provides inadequate evidence with regard to the elevated CVD risk which it may propagate [2–5]. While a notable wealth of evidence exists regarding the prevalence and associated health outcomes of the resilient effects of obesity upon the cardiovascular system in adults, the heterogeneity of studies impedes drawing robust conclusions. Such heterogeneity is primarily attributed to the absence of a uniform set of criteria used to define metabolically healthy obesity, inherently deterring comparability of findings. To this effect, in an effort to standardize the definition "metabolically healthy status", Lavie et al. recently suggested a harmonized definition of metabolically healthy obesity, moving from the more flexible concept of "MetS absence" to a more strict rationale

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; CRP, C-reactive protein; HR, hazard ratio; HOMA-IR, homeostasis model assessment of insulin resistance; MHN, metabolically healthy non-obese; MHO, metabolically healthy obese; MetS, metabolic syndrome; MUN, metabolically unhealthy non-obese; MUO, metabolically unhealthy obese; 95% CI, 95% confidence interval.

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which demands the absence of all MetS criteria excluding waist circumference [6].

Large scale epidemiological studies that have previously used the aforementioned definition have documented prevalence rates ranging between 12% and 17% rate in obese European and American adults [7,8]. Given that in 2016 alone, 650,000 million adults were obese worldwide, along with the ever increasing global obesity trends, it is anticipated that a notable proportion of MHO adults may have not yet fully demonstrated the associated CVD risk incurred by their underlying condition [9]. As of such, to date, the CVD risk stratification in this particular population remains to be elucidated. Furthermore, the constancy of metabolically healthy obesity over time and latency of lag effects also remains uncertain.

The aim of the present work was to evaluate **a.** the prevalence of strictly defined metabolically healthy obesity in a sample of apparently healthy men and women from Greece, **b.** the transition of MHO to MUO status within a 10-year follow-up period and **c.** the 10-year combined CVD risk of MHO individuals over various reference groups. We posed three a priori research hypotheses: **A.** The 10-year combined CVD event risk corresponding to MHO participants will be intermediate to the respective risk of their MHN and MUO counterparts; **B.** Metabolically healthy obesity is not a stable condition; a significant portion of MHO subjects will transient to metabolically unhealthy status within the decade, with this transition increasing their CVD risk; and **C.** Inflammation and insulin resistance will mediate the effect of metabolically healthy obesity on 10-year combined CVD event.

2. Materials/Subjects and Methods

2.1. Study Sample

The ATTICA study is a prospective, observational cohort investigation which was initiated in 2001 [10]. At baseline (2001−2002), $n = 3042$ apparently healthy volunteers residing in the greater metropolitan Athens area, Greece, agreed to participate (75% participation rate). Of the enrolled participants, $n = 1514$ (49.8%) were men (46 ± 13 years) and $n = 1528$ (50.2%) were women (45 ± 14 years). During baseline examination, a detailed clinical evaluation was performed by trained physicians; all participants were free of CVD and other chronic diseases, according to the study protocol. For the scope of the present work, we initially used the $n = 2020$ participants with complete CVD evaluation in the follow-up assessment. Then, for our primary analysis, we excluded $n = 100$ participants who were classified as MHN at the recruitment phase, yet they transitioned to other BMI or metabolic categories within the decade, as well as $n = 30$ participants initially classified as MHO who changed BMI category within the 5-year follow-up period, for a final sample size of $n = 1890$.

2.2. Bioethics

ATTICA study was approved by the Bioethics Committee of Athens Medical School. The study was carried out in accordance with the Declaration of Helsinki (1989) of the World Medical Association. All participants were informed about the study aims and procedures and provided written informed consent.

2.3. Obesity and Metabolic Status Measurements at Baseline Examination

At baseline, obesity and metabolic status was examined in all participants. Weight status was defined using the BMI cut off points recommended by the World Health Organization. BMI was calculated as weight (in kilograms) divided by height (in meters squared). Height was measured to the nearest 0.5 cm, with participants not wearing shoes, their backs square against the measuring wall tape, eyes looking straight ahead, with a right-angled triangle resting on the scalp and against the wall. Weight was measured with a lever balance, to the nearest 100 g, without shoes and in light undergarments. Normal weight was defined as BMI between 18.5 and 25 kg/m^2, overweight as BMI between 25 and 29.9 kg/m^2 and obesity as BMI ≥ 30 kg/m^2. Underweight was defined as BMI < 18.5 kg/m^2.

Metabolic status was defined using the criteria suggested by Lavie et al. [6]. In particular, healthy metabolic status was defined as absence of hypertension, dyslipidemia and glycemic abnormalities. Hypertension was defined as systolic blood pressure ≥130 mm Hg and/or diastolic blood pressure ≥85 mm Hg. Dyslipidemia was defined as triglyceride levels ≥150 mg/dL and/or high density lipoprotein levels <40 mg/dL in men and <50 mg/dL in women. Glycemic abnormalities were defined as fasting glucose ≥100 mg/dL. Drug treatments for the aforementioned conditions were set as alternative indicators of metabolic abnormalities. For the scope of the present work participants were divided in four groups as follows: **a.** MHN defined as BMI < 30 kg/m^2 and healthy metabolic status; **b.** MHO defined as BMI ≥ 30 kg/m^2 and healthy metabolic status; **c.** MUN defined as BMI < 30 kg/m^2 and unhealthy metabolic status; and **d.** MUO defined as BMI ≥ 30 kg/m^2 and unhealthy metabolic status.

2.4. Other Baseline Measurements

The sociodemographic and lifestyle characteristics assessed included age, gender, educational level attained, level of adherence to the Mediterranean diet, physical activity status, and smoking habits. Adherence to Mediterranean diet was assessed through MedDietScore (range 0–55), wherein low adherence to Mediterranean diet was defined as MedDietScore below the median value (i.e. MedDietScore ≤ 27). Regarding biochemical measurements, CRP (mg/L) was measured and used to define low grade inflammation. Insulin resistance was assessed by calculation of a HOMA-IR approach (glucose (mmol/L) × insulin (μU/mL)/22.5). Due to the lack of national thresholds, Receiver Operating Characteristic curves analysis was used to assess the cut-off points of baseline predictors (i.e. HOMA-IR and CRP) with the best discriminative ability (i.e. highest sensitivity and lowest 1-specificity) for the primary endpoint (i.e. 10-year combined CVD event). Thereby, the median values of these markers were revealed as the best cut off values; low grade inflammation was defined as CRP > 1.1 mg/L and insulin resistance as HOMA-IR > 2.78.

Further details regarding the methods and measurements applied have been previously detailed [10].

2.5. Endpoint and Follow-Up Evaluation

Intermediate follow-up (i.e., 5-year) and 10-year follow-up of ATTICA study was performed in 2006 and 2012, respectively. The combined endpoint studied in this work was the development of a fatal or non-fatal CVD event. A CVD event was defined as the development of acute myocardial infarction, or unstable angina, or other identified forms of ischemia (WHO-ICD coding 410–414.9, 427.2, 427.6), or heart failure of different types and chronic arrhythmias (WHO-ICD coding 400.0–404.9, 427.0–427.5, 427.9) or stroke (WHO-ICD coding 430–438). For participants who died during follow-up, information was retrieved from relatives and death certificates. Evaluation of metabolic status was also performed in the aforementioned follow-up periods, while weight status was revaluated only in the intermediate follow-up.

2.6. Statistical Analysis

Categorical variables are presented as absolute (n) and relative frequencies (%). Continuous variables are presented as mean values ± standard deviation. Associations between normally distributed variables and the combined obesity and metabolic status were evaluated through one-way analysis of variance or Student's *t*-test for independent samples. Whether these variables were normally distributed was tested through P-P plot and equality of variances through Levene's test. For non-normally distributed variables, Kruskal-Wallis and Mann-Whitney tests were used. Associations between categorical variables and the combined obesity and metabolic status were tested with the chi-squared test. HRs and their corresponding 95% CIs for the combined obesity and metabolic status in relation to 10-year CVD event were evaluated through multivariable Cox-regression analysis in the total sample, as well as in each of the respective subgroups. Proportional hazards' assumption was graphically tested. Interactions between groups of participants were tested, and when significant the analyses were further stratified. STATA software, version 14 (MP & Associates, Sparta, Greece) was used for all statistical analyses.

3. Results

At baseline, the prevalence of MHO status in the total sample of the ATTICA study was 4.8% ($n = 146$) (4.9% in men and 4.7% in women, $p = 0.198$). Among obese adults, 28.2% presented with a metabolically healthy status at the recruitment phase. For the purposes of the present analysis, only 1890 participants with complete CVD evaluation metrics at 10-year follow-up were retained for further analyses. The 10-year CVD event rate was 15.7% ($n = 299$) [19.7% ($n = 189$) in men and 11.7% ($n = 110$) in women, $p < 0.001$]. Median survival time was 9.7 years in men and 9.8 years in women ($p = 0.55$).

Table 1 depicts the baseline sociodemographic, lifestyle, clinical and biochemical characteristics of study participants according to their combined obesity and metabolic status. MHO participants were almost one decade older compared with their MUO counterparts ($p < 0.001$). As for the lifestyle factors, MHO and MUO subjects presented a similar pattern of unhealthy lifestyle habits, including smoking and sedentary physical activity, yet better than their non-obese metabolically healthy or unhealthy counterparts ($p < 0.001$). However, when it came to the level of adherence to the Mediterranean diet, an inverse association was observed with MHO participants presenting the lowest MedDietScore values ($p < 0.001$). Additionally, regarding insulin resistance, an increasing trend of HOMA-IR was observed passing from MHN to MUO while regarding CRP levels obese participants presented the highest values irrespective of their metabolic status (all $ps < 0.001$).

The 10-year CVD event rate across the combined obesity and metabolic status categories is also presented in Table 1. Unadjusted models revealed that MHO participants presented 2.66 times higher CVD event rate compared with their non-obese counterparts i.e. MHN ($p < 0.001$). On the other side, MHO had from 1.25 to 1.56 lower times likelihood to suffer from CVD within the decade compared with their metabolically unhealthy counterparts, irrespective of their weight status ($p < 0.001$).

The transition of MHO participants to metabolically unhealthy states within the follow up is shown in Table 2. In the 5-year follow-up period, transition to metabolically unhealthy status was observed for 33% of MHO participants. Within the decade, almost half of obese participants who were initially metabolically benign resulted in presenting with MUO. In particular, among this group, 24% achieved the highest disease risk burden, including abnormal glycemic, lipidemic, and blood pressure profiles.

The baseline sociodemographic, lifestyle and clinical characteristics of stable and temporal MHO participants are presented in Table 3. Unadjusted analysis revealed that MHO participants who retained their metabolically healthy status within the decade (i.e. stable) had better lifestyle (i.e. higher adherence to Mediterranean diet and better physical activity status) at the recruitment phase (all $ps < 0.05$). Additionally, temporal MHO subjects presented higher CRP and HOMA-IR values as well as higher low density lipoprotein and systolic blood pressure at baseline compared with their stable MHO counterparts (all $ps < 0.05$).

Table 1
Baseline sociodemographic, lifestyle, clinical and biochemical factors and 10-year cardiovascular disease (CVD) event of apparently healthy participants according to combined obesity and metabolic status ($n = 1890$).

Baseline factors	Combined obesity and metabolic status				p-Value
	MHN	MHO	MUN	MUO	
	$n = 686$	$n = 107$	$n = 672$	$n = 425$	
Age, years	38 (12)	45 (12)	50 (13)	52 (12)	<0.001
Men, %	40	50	54	58	<0.001
Years of school	13 (3)	11 (4)	12 (4)	11 (4)	<0.001
Body mass index, kg/m^2	23.9 (3.06)	32.8 (3.89)	25.5 (2.67)	33.5 (3.17)	<0.001
Waist circumference, cm	82.1 (12.0)	102.1 (14.1)	90.2 (12.2)	108.3 (12.1)	<0.001
Current smoking, %	47	38	42	40	0.024
Physical activity, %	45	27	40	29	<0.001
MedDietScore (range 0–55)	28. 2 (6.8)	21.8 (6.1)	24.9 (5.6)	23.8 (4.6)	<0.001
History of hypertension, %	0	0	69	32	<0.001
Systolic blood pressure, mm Hg	112 (11)	118 (10)	128 (19)	137 (19)	<0.001
History of hypercholesterolemia, %	0	0	73	64	<0.001
Low density lipoprotein, mg/dL	98 (22)	104 (18)	140 (35)	136 (36)	<0.001
High density lipoprotein, mg/dL	55 (14)	52 (12)	46 (15)	44 (12)	<0.001
Triglycerides, mg/dL	81 (30)	122 (28)	138 (107)	158 (91)	<0.001
History of diabetes mellitus, %	0	0	62	38	<0.001
Fasting glucose, mg/dL	86 (12)	87 (12)	95 (25)	104 (35)	<0.001
HOMA-IR	2.59 (0.61)	2.98 (1.55)	3.29 (1.97)	3.87 (3.22)	<0.001
CRP, mg/L	1.51 (2.25)	2.88 (2.84)	1.84 (2.07)	3.21 (3.20)	<0.001
Alanine transaminase, U/L	18.62 (11.54)	28.00 (14.78)	20.08 (11.25)	23.35 (14.34)	<0.001
Aspartate transaminase, U/L	23.77 (11.06)	31.62 (16.38)	24.91 (11.44)	24.74 (10.93)	0.02
Creatinine clearance, mL/min/1.73 m^2	93 (24)	127 (34)	88 (26)	113 (34)	<0.001
Family history of CVD, %	26	25	31	28	0.192
10-year follow-up					
First combined CVD event, %	6	16	20	25	<0.001

Data are presented as mean ± standard deviation (SD) (i.e. mean (SD)). p-Values were obtained using one-way analysis of variance for the normally distributed variables (age, MedDietScore, body mass index), Kruskal-Wallis test for the rest quantitate variables (years of school, waist circumference, systolic blood pressure, fasting glucose, triglycerides, high density lipoprotein, low density lipoprotein, C-reactive protein (CRP), Homeostatic Model Assessment of Insulin Resistance (HOMA-IR)), alanine transaminase, aspartate transaminase, creatinine clearance and chi-squared test for categorical variables. Metabolically healthy non-obese (MHN): BMI < 30 kg/m^2 with metabolically health status; metabolically healthy obese (MHO): BMI ≥ 30 kg/m^2 without metabolically healthy status; metabolically unhealthy non-obese (MUN): BMI < 30 kg/m^2 without metabolically health status; metabolically unhealthy obese (MUO): BMI ≥ 30 kg/m^2 without metabolically healthy status. Metabolically healthy status was defined as the absence of 4 metabolic syndrome components i.e. elevated triglycerides, reduced high density lipoprotein, elevated blood pressure and elevated fasting glucose including the drug treatment for all these conditions.

Table 2
Metabolic status and transition to metabolically unhealthy status in terms of isolated or combined metabolic syndrome (MetS) components in metabolically healthy obese at 5-year and 10-year follow up periods ($n = 107$).

	5-year follow up	10-year follow up
Across follow-up, transition to:		
Diabetes/prediabetes, %	11	24
Hypertension, %	23	45
Dyslipidemia, %	33	52
Metabolically healthy, %	67	48
≥1 MetS component, %	33	52
≥2 MetS components, %	20	30
All 3 MetS components, %	14	24

Metabolically healthy status was defined as the absence of 4 MetS components i.e. elevated triglycerides, reduced high density lipoprotein, elevated blood pressure and elevated fasting glucose including the drug treatment for all these conditions. The examined MetS components within the follow-up periods were as follows: a. diabetes/prediabetes status; b. hypertension and c. dyslipidemia (elevated triglycerides and high density lipoprotein were assessed under this term). To evaluate the prevalence of transition to the aforementioned conditions within the follow-up periods chi-squared tests were performed.

Multivariable Cox regression analysis revealed that the 10-year CVD event HR (95% CI) for obesity (yes vs. no) (not adjusted for metabolic status) was 1.65 (1.00, 2.92). The unadjusted-for-obesity HR (95% CI) corresponding to metabolic status (healthy vs. unhealthy) was 0.44 (0.18, 0.99). In mediation analysis where both obesity and metabolic status were included in the model, the independent effect on 10-year CVD event was retained only for metabolic status (HR = 0.43, 95% CI 0.17, 0.99), yet not for obesity (HR = 1.61 95% CI 0.89, 2.52) (data not shown).

Table 3
Baseline sociodemographic, lifestyle, clinical and biochemical factors and 10-year cardiovascular disease (CVD) event of apparently healthy participants with stable vs. temporally metabolically benign obesity ($n = 107$).

Baseline factors	10-year metabolically healthy obesity		*p*-Value
	Stable	Temporal	
	$n = 51$	$n = 56$	
Age, years	42 (12)	46 (12)	0.09
Men, %	54	39	<0.001
Years of school	13 (3)	11 (4)	0.62
Body mass index, kg/m^2	32.3 (1.85)	33.3 (2.97)	0.06
Waist circumference, cm	100 (20)	106 (11)	0.14
Current smoking, %	42	40	0.47
Physical activity, %	45	39	0.03
MedDietScore (range 0–55)	25.6 (4.6)	19.1 (5.7)	<0.001
Systolic blood pressure, mm Hg	114 (11)	121 (12)	<0.001
Low density lipoprotein, mg/dL	95 (21)	110 (25)	<0.001
High density lipoprotein, mg/dL	50 (14)	48 (15)	0.76
Triglycerides, mg/dL	118 (20)	130 (25)	<0.001
Fasting glucose, mg/dL	85 (13)	90 (12)	0.08
HOMA-IR	2.6 (0.6)	3.2 (1.9)	<0.001
CRP, mg/L	2.41 (2.45)	2.94 (2.27)	0.01
Alanine transaminase, U/L	27.96 (14.49)	29.34 (10.30)	0.71
Aspartate transaminase, U/L	29.20 (10.60)	34.19 (12.44)	0.63
Creatinine clearance, mL/min/1.73 m^2	120 (26)	129 (29)	0.12
Family history of CVD, %	23	32	0.004
10-year follow-up			
First combined CVD event, %	9	25	0.05

Data are presented as mean ± standard deviation (SD) (i.e. mean (SD)). *p*-Values were obtained using Student's *t*-test for independent samples for the normally distributed variables (age, MedDietScore, body mass index), Mann Whitney test for the rest quantitate variables (years of school, waist circumference, systolic blood pressure, fasting glucose, triglycerides, high density lipoprotein, low density lipoprotein, C-reactive protein (CRP), Homeostatic Model Assessment of Insulin Resistance (HOMA-IR)), alanine transaminase, aspartate transaminase, creatinine clearance and chi-squared test for categorical variables. Metabolically healthy non-obese (MHN): BMI < 30 kg/m^2 with metabolically health status; metabolically healthy obese (MHO): BMI ≥ 30 kg/m^2 without metabolically healthy status. Metabolically healthy status was defined as the absence of 4 metabolic syndrome components i.e. elevated triglycerides, reduced high density lipoprotein, elevated blood pressure and elevated fasting glucose including the drug treatment for all these conditions.

Nested Cox regression models to evaluate the association of the combined obesity and metabolic status on 10-year CVD event are presented in Table 4. In the unadjusted models, MHO participants presented almost 89% significantly higher risk for developing 10-year CVD events, as compared to their MHN counterparts ($p < 0.001$). In the age- and gender-adjusted model this association was attenuated yet remained significant. However, after adjusting for lifestyle, clinical, and biochemical markers, MHO status retained its aggravating effect yet it did not reach the level of significance. Models were additionally rerun setting MHO participants as a reference group; no significant differences were observed with their MUO and MUN counterparts against 10-year CVD event in the fully adjusted model [HR, 95% CI: 1.51 (0.52, 4.41) and 1.32 (0.25, 5.14), respectively] (data not shown). On the other hand, non-persistent MHO status (i.e. transition from MHO to MUO) was independently associated with elevated CVD risk compared with the MHN counterpart even in the fully adjusted model. Moreover, sensitivity analysis excluding overweight subjects was performed; even in this case all the aforementioned trends were sustained (data not shown).

In the formal analysis of interaction, little evidence of significant heterogeneity was produced (all *ps* for interaction >0.10) apart from gender, MedDietScore, CRP, and HOMA-IR. Thereby, stratified analyses were performed using these variables as strata and the respective results are presented in Table 5. It was revealed that MHO status was positively associated with 10-year CVD event only in women, participants with low adherence to Mediterranean diet, as well as those with HOMA-IR and CRP values above respective median values (all $ps < 0.05$).

4. Discussion

4.1. Principle Findings

In the present work, approximately half of MHO individuals developed a metabolically unhealthy status within the decade and subsequently exhibited high CVD risk, comparable to that of baseline MUO participants. Furthermore, the aggravating effect of obesity even resilient to metabolic abnormalities was stronger for women, and particularly among those with unhealthy dietary habits, namely including low adherence to the Mediterranean diet. It is noteworthy that low grade inflammation and insulin resistance presented significant interacting effects with the combined obesity and metabolic status upon the long-term risk of CVD. Hence, these findings suggest that such markers may predict individuals with intermediate metabolic conditions who are at highest risk of developing CVD.

4.2. Metabolically Healthy Obesity and CVD

Previous studies have provided inconsistent results regarding MHO individuals' CVD risk. The heterogeneity of findings is mainly attributed to the fact that a common set of criteria defining this intermediate condition has not been uniformly employed. In fact, the vast majority of prospective studies conducted to date define MHO status as a condition which does not meet MetS criteria. Hence, in many cases, obese subjects with even 2 metabolic abnormalities could be misclassified as being "healthy". In such studies, the association of MHO condition with long-term CVD incidence varied from being non-existent [11–14] to positive [15–17] when compared with MHN status.

Most recently, the use of a uniform clearly defined characterization of MHO (namely the absence of all MetS abnormalities) has been employed. To this effect, visceral adiposity is excluded from eligibility criteria since most obese individuals have waist circumference levels above the normal range [5]. Evidence arising from longitudinal prospective studies employing such patient criteria [18–21] reveals that obese individuals exhibit an elevated CVD risk, independently of their

Table 4
Nested Cox-regression analysis models to evaluate the association of combined obesity and metabolic status with 10-year cardiovascular disease (CVD) event ($n = 1890$).

	Model 1	Model 2	Model 3	Model 4	Model 5
Combined obesity and metabolic status					
MHN	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
MHO	**1.89 (1.24, 2.87)*****	**1.37 (1.00, 2.17)****	**1.26 (0.99, 2.03)↑**	**1.07 (0.98, 2.37)↑**	**0.95 (0.37, 2.08)**
MHO to MUO	**2.76 (2.01, 3.40)*****	**1.81 (1.22, 2.55)****	**1.82 (1.25, 2.63)***	**1.83 (1.24, 2.69)***	**1.43 (1.02, 2.01)***
MUN	2.39 (1.67, 3.10)	1.81 (1.26, 2.60)	1.73 (1.16, 2.86)	1.72 (1.03, 2.87)	1.45 (0.85, 2.50)
MUO	2.93 (2.05, 3.37)	2.73 (1.85, 3.22)	2.54 (1.55, 3.10)	2.41 (1.42, 3.08)	2.04 (1.15, 2.89)
Age, per 1 year	–	1.08 (1.07, 1.09)	1.08 (1.06, 1.09)	1.07 (1.05, 1.09)	1.07 (1.05, 1.09)
Male gender	–	1.86 (1.41, 2.46)	1.82 (1.36, 2.45)	1.81 (1.17, 2.76)	1.66 (1.07, 2.61)
Years of school, per 1 year	–	–	0.96 (0.92, 0.99)	0.97 (0.92, 1.02)	0.95 (0.90, 1.01)
MedDietScore (range 0–55), per 1/55	–	–	0.98 (0.96, 0.99)	0.98 (0.94, 0.99)	0.97 (0.94, 1.01)
Physical activity, yes vs. no	–	–	0.94 (0.70, 1.25)	1.32 (0.88, 1.98)	1.43 (0.94, 2.17)
Current smoking, yes vs. no	–	–	1.27 (0.94, 1.71)	1.50 (1.00, 2.28)	1.45 (0.94, 2.23)
LDL, per 1 mg/dL	–	–	–	1.01 (1.00, 1.03)	1.00 (0.99, 1.01)
Family history of CVD, yes vs. no	–	–	–	1.37 (0.90, 2.08)	1.39 (0.89, 2.17)
ALT, per 1 U/L	–	–	–	1.01 (0.98, 1.04)	1.00 (0.97, 1.04)
AST, per 1 U/L	–	–	–	0.99 (0.95, 1.02)	0.98 (0.94, 1.01)
$C_{(CR)}$, per 1 mL/min/1.73 m^2	–	–	–	0.99 (0.98, 1.01)	0.99 (0.98, 1.01)
Waist circumference, per 1 cm	–	–	–	–	1.00 (0.98, 1.02)
HOMA-IR, per 1 unit	–	–	–	–	1.06 (0.98, 1.16)
CRP, per 1 mg/L	–	–	–	–	1.06 (0.98, 1.15)

MHN: BMI < 30 kg/m^2 with metabolically health status; MHO: BMI ≥ 30 kg/m^2 without metabolically healthy status; MUN: BMI < 30 kg/m^2 without metabolically health status; MUO: BMI ≥ 30 kg/m^2 without metabolically healthy status. Metabolically healthy status was defined as the absence of 4 metabolic syndrome components i.e. elevated triglycerides, reduced high density lipoprotein, elevated blood pressure and elevated fasting glucose including the drug treatment for all these conditions. Abbreviations: alanine transaminase (ALT); aspartate transaminase (AST); C-reactive protein (CRP); creatinine clearance ($C_{(CR)}$); Homeostatic Model Assessment of Insulin Resistance (HOMA-IR); low density lipoprotein (LDL); metabolically healthy non-obese (MHN); metabolically healthy obese (MHO); metabolically unhealthy non-obese (MUN); metabolically unhealthy obese (MUO). ***p-value < 0.001; **p-value < 0.01; *p-value < 0.05; ↑p-value < 0.10

metabolic profile. In the present work, where a strict definition for MHO participants was used, an aggravating effect of obesity metabolically benign status on 10-year CVD risk was not revealed. This supports the hypothesis that MHO status is not as low risk as speculated while at the same time this non-significant association may imply the existence of conditions with strong mediating or moderating effect.

In addition, as it is equivocally important to appropriately define the reference groups for comparisons [22], it is useful to emphasize some additional findings arising from the present work. First, MHO subjects were examined against their "persistent" MHN counterparts, drawing conclusions after a comparison with the "healthiest" group. Second, MHO subjects were also examined against their MUO and MUN counterparts, yet they did not seem to exert significantly different CVD risk.

4.3. Progression from Metabolically Benign to Unhealthy Obesity Status

Most recently, it is conferred that MHO status may be transient in nature. Prospective population-based studies have revealed that a considerable proportion, ranging between 33 and 52%, of MHO individuals lose such status over time [11,14,23]. However, these rates have been mainly documented in MHO subjects with ≤2 metabolic abnormalities. It is upheld, that these estimates may underestimate true rates as individuals with two established unhealthy conditions are more likely to be diagnosed with MetS the following years. On the other hand, the transition of obese individuals without metabolic abnormalities has scarcely been investigated. In the present work, MHO participants without metabolic abnormalities at baseline subsequently progressively increased likelihood to present at least one metabolic abnormality within the 10-year follow-up period (Table 2). This is in line with the hitherto evidence yet comes to highlight that even the "healthiest" obese confer a high risk to develop conventional risk factors and become MUO later in their life.

On the other hand, little evidence exists regarding CVD risk of non-persistent MHO persons. In the present work, this MHO subgroup was independently associated with increased CVD risk within the decade, strengthening the hypothesis that the initially observed non-significant outcomes might be hindered by a lag in risk till the transition to unhealthy metabolic status. This outcome is not entirely consistent with the few previous works that have examined this issue. For instance, our results are in line with a very recent work from Multi-Ethnic Study of Atherosclerosis [14], yet in North West Adelaide Health Study no significant differences were observed [11]. However, MHO status in these studies was differentially defined yet other methodological variations may partially explain these inconsistencies. The aforementioned findings come to support the hypothesis that metabolic abnormalities may indicate a threshold of cumulative obesity exposure translated to CVD risk. In accordance with this, in the present work metabolic status was a strong confounder in the obesity-CVD event association, suggesting that the aggravating effect of excess body weight is largely attributed to the metabolic landscape.

4.4. Low Grade Inflammation and Insulin Resistance: The Role of Surrogate Markers in CVD Risk of MHO Subjects

In the present work, the potential mediating effect of socio-demographic, lifestyle and biochemical factors was also examined. An important observation here was that MHO persons with low grade inflammation and/or insulin resistance had significantly higher 10-year CVD risk compared with their MHO counterparts without these metabolic abnormalities. Inflammation and insulin resistance are two often-discussed points in MHO status [24]. When assessing such intermediate risk populations, the usefulness of conventional risk factors is questionable. Hence, subclinical conditions and surrogate CVD markers may be of more accurate predictive ability. In this context, CRP and HOMA-IR have been suggested to be used as markers to define the metabolic profile of apparently healthy obese yet with non-conclusive remarks. Interestingly, in a proteomics study MHO women had lower levels of pro-inflammatory (e.g., CRP) and higher levels of anti-inflammatory biomarkers compared with their MUO controls [25]. On the other side, recent outcomes from the European Prospective Investigation of Cancer study suggested that within the MHO group, CRP-defined low grade inflammation was associated with a higher risk for coronary heart disease [26]. A few studies have included CRP in the definition of MHO status, yet not under the context of the aforementioned strict criteria, which may have biased findings towards the

Table 5
Sensitivity analyses to evaluate the association of combined metabolic- and obesity-related status with 10-year cardiovascular disease event ($n = 1890$).

	Combined obesity and metabolic status	Hazard ratio	95% confidence interval
Gender (n/cases)			
Men (941/189)	MHN	1.00	Ref
	MHO	1.09	0.35, 3.36
	MUN	**1.92**	**1.06, 3.48**
	MUO	**2.64**	**1.42, 4.91**
Women (949/110)	MHN	1.00	Ref
	MHO	**2.01**	**1.34, 3.49**
	MUN	1.42	0.50, 4.04
	MUO	**2.07**	**1.06, 3.79**
p for interaction = 0.05			
Level of adherence to Mediterranean diet, MedDietScore, range 0–55 (n/cases)			
MedDietScore > 27 (732/28)	MHN	1.00	Ref
	MHO	1.10	0.53, 3.47
	MUN	1.63	0.86, 3.52
	MUO	1.98	1.11, 4.12
MedDietScore ≤ 27 (1158/271)	MHN	1.00	Ref
	MHO	**1.14**	**1.00, 2.35**
	MUN	**1.73**	**1.02, 2.93**
	MUO	**2.35**	**1.37, 4.03**
p for interaction = 0.01			
CRP categories (n/cases)			
CRP ≤ 1.1 mg/L (957/120)	MHN	1.00	Ref
	MHO	0.72	0.31, 3.24
	MUN	0.82	0.31, 2.26
	MUO	0.61	0.13, 2.90
CRP > 1.1 mg/L (933/179)	MHN	1.00	Ref
	MHO	**1.25**	**1.08, 3.26**
	MUN	**2.17**	**1.12, 4.20**
	MUO	**3.56**	**1.88, 4.77**
p for interaction = 0.001			
HOMA-IR categories (n/cases)			
HOMA-IR ≤ 2.78 (937/101)	MHN	1.00	Ref
	MHO	1.42	0.51, 4.01
	MUN	1.06	0.36, 3.14
	MUO	2.36	0.77, 4.25
HOMA-IR > 2.78 (953/198)	MHN	1.00	Ref
	MHO	**1.75**	**1.20, 3.76**
	MUN	**1.99**	**1.09, 3.61**
	MUO	**2.49**	**1.35, 4.62**
p for interaction = 0.001			

All models were adjusted for age, educational status, physical activity, current smoking, low density lipoprotein levels, family history of cardiovascular disease, alanine transaminase, aspartate transaminase and creatinine clearance. **Bold** indicates estimates that are significantly different from the reference group at $p < 0.05$. Abbreviations: C-reactive protein (CRP); Homeostatic Model Assessment of Insulin Resistance (HOMA-IR); metabolically healthy non-obese (MHN); metabolically healthy obese (MHO); metabolically unhealthy non-obese (MUN); metabolically unhealthy obese (MUO).

null [13,27]. As for insulin resistance, this has been used as an additional criterion for MHO status, yet with mixed outcomes regarding the observed long-term CVD risk [18,28]. Considering the observation in the present work, the added value of a definition inclusive of insulin resistance and/or vascular inflammation in concert with stricter criteria for metabolic abnormalities should be further explored [22]. Along with these findings, in the current literature, it has been suggested that surrogate markers i.e. redox stress, small dense low density lipoprotein particles, hepatic enzymes, may largely differentiate MHO from MUO subjects and probably these may possess a better discriminative ability against CVD onset in this intermediate condition [29–32].

4.5. The Gender-Related Gap in MHO Status

An additional gap in knowledge is potential differences in MHO between genders. Interestingly, in the present work significant gender-related interactions were observed with stratified analysis revealing that MHO status was an independent CVD risk factor only in women. This finding contradicts a previous report suggesting a more pronounced aggravating effect in case of men [19]. However, as the only group that directly addressed the question of transition of MHO to MUO status separately in women, Eckel et al. found that a large proportion of metabolically healthy women converted to an unhealthy phenotype over time which then was associated with increased CVD risk [20]. In line with this, here, the men-to-women MHO-to-MUO transition rate was 0.81 i.e. in favor of women. The mechanisms through which this observation may be exerted are unclear; genetic, anatomic, physiologic, metabolic and hormonal differences along with psychosocial and lifestyle determinants may explain this heterogeneity [33,34].

4.6. The Mediating Effect of Nutritional Habits in MHO subjects' CVD Risk

Adherence to Mediterranean diet was also suggested as an important lifestyle mediator; suggesting that MHO participants with low adherence to Mediterranean diet were independently associated with elevated CVD risk. This finding corroborates with previous literature reports [35]. A potential mechanism here could be the prevention of transition to metabolically unhealthy status driven by the cardioprotective properties of this dietary pattern, yet the exact underlying paths remain to be clarified [36,37].

4.7. Limitations and Strengths

The present findings should be interpreted with caution given the observational study design employed. The principle hypothesis examined here was related with an intermediate condition. The vast majority of intermediate forms of disease do not strictly correspond to a well-defined phenotype which may be a matter of confusion. Additionally, even if the bias attributed to the transition to other BMI or metabolic status categories was partially avoided, misclassification of transitions cannot be precluded due to the extended interim periods between follow-up assessments.

The aforementioned limitations are compensated for several strengths as well as a novel approach employed. First of all, to the best of our knowledge this in one of the very few prospective studies that evaluated the transition of MHO to MUO status and associated this transition with 10-year CVD risk, under the context of a strict definition regarding metabolic status. Moreover, the present work provided additional evidence that low grade inflammation and insulin resistance may ameliorate the risk classification of MHO participants. Lastly, this work revealed outcomes from extensive sensitivity analyses; **a.** in the primary analysis, only "persistent" MHN were set as reference group; **b.** the observed trends were re-examined in the context of different comparison groups i.e. with and without overweight participants and with MHO status as reference group; and **c.** significant interactions with demographic, lifestyle and clinical factors were extensively assessed, accompanied by stratified analyses.

4.8. Conclusions

While ever increasing efforts have sought to elucidate the health outcomes of metabolically benign obesity and the underlying paths, clinical recommendations and public health intervention remain to be guided with appropriate conclusive evidence [38]. Our work sought to address these gaps in knowledge builds in the following key areas. First, our findings suggest that primary prevention strategies and constant vigilance may be necessary in MHO persons so as to deter transitions to MetS and subsequent increased CVD risk. Concomitantly, our findings suggest that further efforts should focus on apparently "persistent" MHO subjects. In light of this perspective, appropriately defining the subset of obese persons who are "over time" resilient to metabolic abnormalities, as well as identifying their particular features, is mandated for identifying those at lowest risk of adverse health outcomes, including CVD.

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Declarations of Interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.metabol.2019.01.003.

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