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ORIGINAL RESEARCH

Different Metabolic Phenotypes of Obesity and 2 Decades Risk of Cardio–Renal–Metabolic Multimorbidity: Tehran Lipid and Glucose Study

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BACKGROUND: Less is known regarding the association between metabolic phenotypes of general and abdominal obesity and incident cardio–renal–metabolic (CRM) multimorbidity, defined as coexistence of at least 2 of the following: diabetes, chronic kidney disease, and cardiovascular diseases (hypertension or stroke or coronary heart disease).

METHODS: Among 6343 participants (3555 women), with a mean age of 37.06 years, metabolically healthy status was defined as absence of any metabolic syndrome components. Participants were classified as metabolically healthy/unhealthy normal weight, overweight, and obese on the basis of body mass index; and metabolically healthy/unhealthy nonabdominal obese and abdominal obese according to waist circumference. Multivariable Cox hazards regression models were used to estimate hazard ratios (HRs) and 95% CIs, adjusted for age, sex, smoking status, education level, marital status, pulse rate, estimated glomerular filtration rate, family history of premature cardiovascular disease, and family history of diabetes.

RESULTS: During a median follow-up of 14.3 years, CRM multimorbidity occurred in 4.8, 13.4, 15.0, 10.8, 17.4, and 29.9% of participants with metabolically healthy normal weight, metabolically healthy overweight, metabolically healthy obese, metabolically unhealthy normal weight, metabolically unhealthy overweight, and metabolically unhealthy obese phenotypes, respectively. In multivariable analyses, compared with the metabolically healthy normal weight, participants with metabolically healthy overweight (HR, 2.08 [95% CI, 1.35–3.20]), metabolically healthy obese (HR, 2.04 [95% CI, 1.11–3.75]), metabolically unhealthy normal weight (HR, 2.29 [95% CI, 1.61–3.27]), metabolically unhealthy overweight (HR, 2.83 [95% CI, 2.01–3.99]), and metabolically unhealthy obese (HR, 5.16 [95% CI, 3.64–7.32]) phenotypes had higher risk of developing CRM multimorbidity. Compared with the metabolically healthy abdominal obese phenotype, participants with metabolically healthy nonabdominal obese (HR, 1.77 [95% CI, 1.19–2.64)], metabolically unhealthy nonabdominal obese (HR, 1.95 [95% CI, 1.48–2.57]), and metabolically unhealthy abdominal obese (HR, 3.26 [95% CI, 2.49–4.28]) exhibited elevated risk. Generally, we found no statistically significant effect modification by sex and age; however, these associations were more pronounced among women and younger individuals.

CONCLUSIONS: Our results indicate that there is no benign phenotype of obesity beyond metabolically healthy normal weight regarding the incidence of CRM multimorbidity.

Key Words: metabolic syndrome ■ multimorbidity ■ noncommunicable diseases ■ obesity

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CLINICAL PERSPECTIVE

What Is New?

- Irrespective of metabolic status, having either a body mass index ≥25 kg/m^2 or abdominal obesity is associated with the incidence of cardio–renal–metabolic multimorbidity, suggesting that no benign phenotype of overweight and obesity exists.

What Are the Clinical Implications?

- Abnormal phenotypes may be more strongly associated with cardio–renal–metabolic multimorbidity among women and younger individuals.
- Maintaining a normal weight without any components of metabolic syndrome may be essential for preventing the development of cardio–renal–metabolic multimorbidity.

Nonstandard Abbreviations and Acronyms

2h-PG	2-hour postchallenge glucose
CRM	cardio–renal–metabolic
FPG	fasting plasma glucose
MHAO	metabolically healthy abdominal obesity
MHNAO	metabolically healthy non-abdominal obesity
MHNW	metabolically healthy normal weight
MHO	metabolically healthy obesity
MHOW	metabolically healthy overweight
MUAO	metabolically unhealthy abdominal obesity
MUNW	metabolically unhealthy normal weight
MUNAO	metabolically unhealthy nonabdominal obesity
MUO	metabolically unhealthy obesity
MUOW	metabolically unhealthy overweight
NCD	noncommunicable diseases
T2D	type 2 diabetes
TLGS	Tehran Lipid and Glucose Study
WC	waist circumference

Noncommunicable diseases (NCDs) have become a significant global health concern in recent decades, accounting for ≈74% of global deaths.[1] Notably, more than three quarters of these deaths, including 86% of the 17 million premature deaths occurring among individuals aged ≤70 years, take place in low- and middle-income countries.[1] The World Health Organization defines multimorbidity as the coexistence of ≥2 chronic diseases within the same individual,[2] an increasingly prevalent phenomenon in low- and middle-income countries.[3] Cardiovascular diseases (CVDs), chronic kidney disease (CKD), and type 2 diabetes (T2D) often cluster together over a lifetime due to shared genetic and environmental factors, and recognized as the cardio–renal–metabolic (CRM) multimorbidity.[4–8] In the Middle East and North Africa region, nearly one third of the population is reportedly affected by multimorbidity,[9] underscoring the urgent need for global attention and targeted interventions.

In recent decades, obesity has become a global pandemic, with an ongoing rise in prevalence.[10–12] Accordingly, from 2000 to 2019, global disability-adjusted life years related to general obesity rose by 0.48% annually.[10] Moreover, both general and abdominal obesity are recognized as predisposing factors for the components of CRM multimorbidity.[13–15] A pooled cohort study including >120 000 participants from the United States and Europe has noted that the risk of incident cardiometabolic multimorbidity increased by 2- to 10-fold across the body mass index (BMI) spectrum, corresponding to overweight and severe obesity, respectively.[16] On the other hand, several studies have suggested that abdominal obesity may serve as a better indicator of obesity-related conditions, such as cardiometabolic diseases and death, compared with general obesity.[17–19] Recently, a nationwide longitudinal cohort study involving 7597 Chinese adults demonstrated that abdominal obesity is associated with a 74% increased risk of incident cardiometabolic multimorbidity.[20]

While there is a well-established linkage between general/abdominal obesity and metabolic abnormalities,[15,21] a sizeable minority of individuals with obesity do not experience the expected metabolic complications.[22] Conversely, a portion of individuals without obesity exhibit metabolic abnormalities commonly related to obesity.[23] This complexity has led to the notion of metabolic phenotypes of obesity, including metabolically healthy/unhealthy normal weight (MHNW/MUNW), overweight (MHOW/MUOW), and obese (MHO/MUO) on the basis of the BMI levels; as well as metabolically healthy/unhealthy nonabdominal obese (MHNAO/MUNAO) and abdominal obese (MHAO/MUAO) according to waist circumference (WC).[22]

Of note, substantial heterogeneity exists in the literature regarding the association between specific phenotypes, particularly MHOW, MHO, MHAO and MUNW, and the incidence of NCDs.[24–26] A recent systematic review and meta-analysis on 8 studies, found 95.1%, 42.8%, and 90.9% heterogeneity among the literature regarding the association between MHO, MUNW, and MUO phenotypes and incident CKD, respectively.[24] Similarly, another meta-analysis that included 23 studies observed >90% heterogeneity

regarding the association between the MHOW and MHO phenotypes and incident CVD.[25] Also, significant heterogenicity exists regarding the association between MHO, MUOW, and MUO phenotypes with diabetes,[27] as well as the association between MHO and MUNW and incident hypertension.[28] Notably, the definition of MHO phenotype varies extensively in different studies, from having 0 to ≤2 metabolic abnormalities.[25] Of note, while the association between obesity phenotypes and NCDs, individually, is widely reported, less is known regarding incident multimorbidity.

Previously, we have demonstrated that in contrast to men, the MHO phenotype, as well as metabolically unhealthy phenotypes among women, were associated with a nearly 2-fold increased risk of incident hypertension compared with the MHNW phenotype.[29] In the current study, we aimed to evaluate the association between metabolic phenotypes of both abdominal and general obesity and the 2-decade risk of incident CRM multimorbidity—defined as the coexistence of at least 2 of the following: CVD (hypertension, or coronary heart disease [CHD], or stroke), CKD, and T2D.

METHODS

Study Design

This prospective study is part of the TLGS (Tehran Lipid and Glucose Study), a large-scale population-based cohort designed to investigate the burden, risk factors, and outcomes of NCDs. The study commenced in 2 phases: phase 1 (1999–2001; n=15 005) and phase 2 (2002–2005; n=3550). Follow-up examinations were conducted every 3 years in subsequent phases: phase 3 (2005–2008), phase 4 (2009–2011), phase 5 (2012–2015), and phase 6 (2015–2018). The rationale and protocols of the TLGS have been detailed in previous publications.[30] The institutional review board of the Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran, approved the proposal for the current study. Written informed consent was obtained from all participants, and the study was conducted in accordance with the principles of the Declaration of Helsinki and other relevant ethical standards. This manuscript has been prepared in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology checklist.[31] The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Population

In the current study, of the 12 803 participants (10 368 from phase 1 and 2435 from phase 2) aged ≥20 years, we excluded 3955 and 657 participants with prevalent NCDs and unknown baseline status of NCDs (T2D, CVD, CKD, and cancer) respectively, as well as 271 participants who were underweight (BMI <18.5 kg/m^2). Additionally, we excluded 238 participants due to missing data on obesity indices (ie, weight, height, and WC), metabolic indices (fasting glucose, blood pressure, and lipid profiles), covariates, and 1339 participants without any follow-up information to ascertain CRM multimorbidity, leaving, 6343 participants (3555 women) for the analyses (Figure 1).

Clinical and Laboratory Measurements

A trained interviewer conducted interviews with each participant to collect sociodemographic information, including marital status, educational level, smoking status, medication history, past medical history, and family history of diabetes and CVD, using standardized questionnaires. Anthropometric measurements were taken in a standard position, with participants wearing light clothing. WC was measured at the umbilical level. BMI was calculated as weight (kg) divided by height squared (m^2). Systolic and diastolic blood pressures (SBP and DBP, respectively) were measured twice in the sitting position after 15 minutes of rest using a standardized mercury sphygmomanometer (calibrated by the Institute of Standards and Industrial Research). The mean values of these measurements were used in the analysis. The pulse rate was assessed through radial pulse palpation over 1 minute.

Laboratory analyses were conducted after 12 to 14 hours of fasting, using venous blood samples collected between 7:00 and 9:00 AM. All samples were analyzed on collection day at the TLGS research laboratory. Triglycerides, fasting plasma glucose (FPG), 2-hour postchallenge glucose (2h-PG), and total cholesterol were measured using the enzymatic colorimetric method with glycerol phosphate oxidase, glucose oxidase, and cholesterol esterase/oxidase, respectively. High-density lipoprotein cholesterol was measured after precipitating apolipoprotein B–containing lipoproteins with phosphotungstic acid. An oral glucose tolerance test was performed by obtaining blood samples 2 hours after participants consumed an 82.5-g glucose monohydrate solution. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.

Definition of Terms

A positive family history of diabetes was defined as the presence of diabetes in any first-degree relative. A positive family history of CVD was defined as a history of CHD or stroke in first-degree relatives aged <55 years for men and <65 years for women. Smoking status was categorized into 3 groups: never smokers, former smokers, and current smokers. Educational attainment

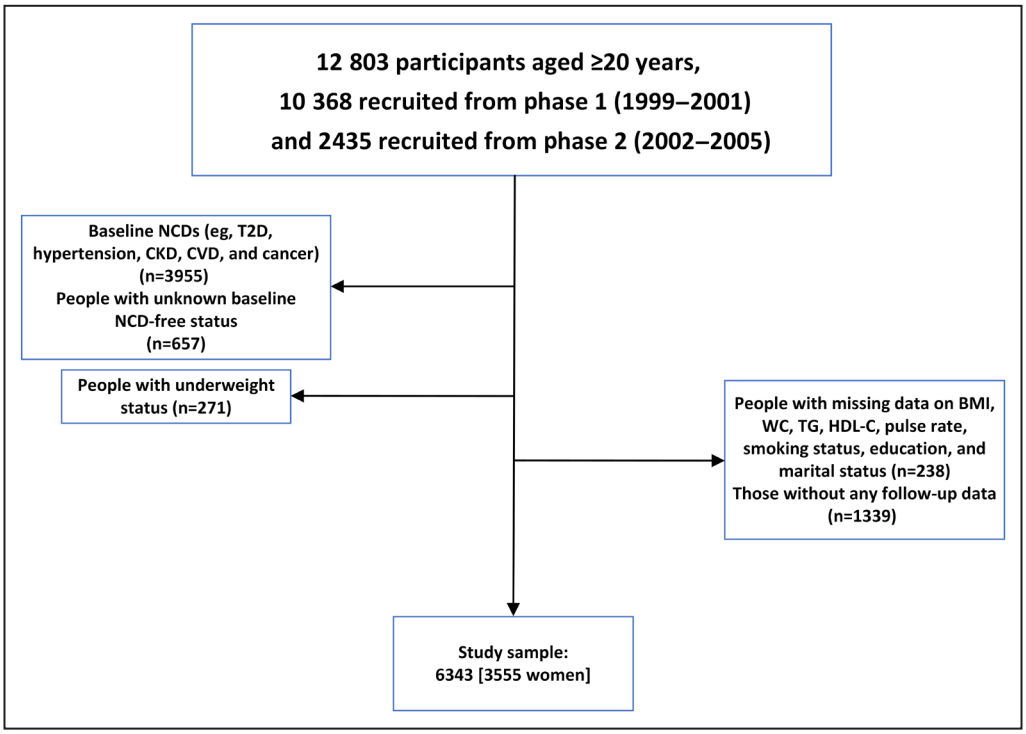

Figure 1. Flowchart of sample selection for the study, the TLGS study, 1999 to 2018.
BMI indicates body mass index; CVD, cardiovascular diseases; HDL-C, high-density lipoprotein cholesterol; NCD, noncommunicable disease; T2D, type 2 diabetes; TG, triglyceride; TLGS, Tehran Lipid and Glucose Study; and WC, waist circumference.

was grouped as follows: <6 years, 6 to 12 years, and >12 years of education. Marital status was classified as either married or unmarried (including single, widowed, or divorced individuals).

General obesity status was classified according to the World Health Organization criteria for adults: normal weight (BMI <25 kg/m^2), overweight (BMI 25 kg/m^2 to <30 kg/m^2), and obesity (BMI ≥30 kg/m^2). Abdominal obesity was determined using country- and population-specific cutoff points, with WC ≥89 cm among men and ≥91 cm among women.[32] According to the Joint Interim Statement,[33] metabolic syndrome components were defined as follows: (1) triglycerides ≥150 mg/dL or the use of lipid-lowering medications; (2) SBP ≥130 mm Hg or DBP ≥85 mm Hg, or the use of antihypertensive medications; (3) FPG ≥100 mg/dL or treatment for diabetes; and (4) high-density lipoprotein cholesterol <40 mg/dL for men and <50 mg/dL for women. Accordingly, we determined metabolic phenotypes of obesity by 3 different definitions:

1. As the first definition, metabolically healthy status was defined as having no abnormality in any of the aforementioned metabolic factors, and considering different BMI levels, 6 metabolic phenotypes of general obesity were determined as MHNW, MHOW, MHO, MUNW, MUOW, and MUO.
2. The second definition was similar to the first definition, with considering metabolically healthy condition as having ≤1 metabolic abnormality.
3. The third definition was similar to the first definition, using WC instead of BMI to define obesity, and participants were categorized as MHNAO, MHAO, MUNAO, and MUAO.

Unless otherwise specified, results in the present study are reported on the basis of the first definition. A telephone interviewer contacted each participant annually to inquire about all interim hospital admissions and deaths. When necessary, trained physicians collected additional information through home/hospital visits, verbal autopsies, hospital records, and death certificates. Events were adjudicated by the Cohort Outcome Committee, which included an internist, an endocrinologist, a cardiologist, a pathologist, an epidemiologist, and other relevant experts as needed. Detailed information regarding the adjudication of outcomes has been published elsewhere.[34]

T2D was defined as having a 2h-PG level ≥11.1 mmol/L (200 mg/dL), or FPG ≥7.0 mmol/L (126 mg/dL), or the use of glucose-lowering medications. If 2h-PG data were unavailable, an FPG level

<5.05 mmol/L (90.9 mg/dL) was considered indicative of a diabetes-free condition.[35] Hypertension was defined as using antihypertensive medications or having an SBP ≥140 mm Hg or DBP ≥90 mm Hg. CKD was defined as an eGFR of <60 mL/min per 1.73 m^2. CVD events, including unstable angina, probable myocardial infarction, definite myocardial infarction, angiographically confirmed CHD, stroke, and cardiovascular-related death, were classified using the *International Classification of Diseases*, *Tenth Revision* (*ICD-10*).

CRM multimorbidity was defined as having ≥2 NCDs including CVD (CHD, stroke, or hypertension), CKD, and T2D.[7,36–40] For each individual condition (CVD, CKD, or T2D), only its first occurrence during follow-up was counted as an incident case of that specific morbidity. We included hypertension within the broader category of CVD due to its well-established pathophysiological role and its shared clinical characteristics and management strategies with other CVD conditions, such as CHD and stroke.[41]

Statistical Analysis

Baseline characteristics of participants, both overall and according to different metabolic phenotypes of obesity, as well as between respondents (individuals included in this study) and nonrespondents (those who were missing data or lost to follow-up), are presented as frequency (%); mean±SD; or median (interquartile range) for categorical variables, normally distributed continuous variables, and skewed continuous variables, respectively. χ^2 tests, Student's *t* test, and Kruskal–Wallis tests were used to compare baseline characteristics among groups, as appropriate.

Cox regression was performed to calculate hazard ratios (HRs) and 95% CIs for CRM multimorbidity events across metabolically healthy and unhealthy obesity phenotype groups. Incrementally adjusted models were constructed as follows: an unadjusted model (model 1); model 2 adjusted for sex and age; and model 3 adjusted for model 2 plus smoking status, educational level, marital status, pulse rate, eGFR, family history of premature CVD, and family history of diabetes.

For diabetes, hypertension, and CKD, the event date was defined as the midpoint between the first follow-up visit when the outcome was identified and the last follow-up visit preceding the diagnosis. For CVD, the event date was determined on the basis of the exact date of diagnosis. The time of CRM multimorbidity occurrence was established as the time of the second NCD diagnosis. Participants who were lost to follow-up, died, or reached the end of the study in 2018 were considered censored. The duration between the study entry and the occurrence of incident CRM multimorbidity or censoring (whichever came first) was defined as the follow-up time. In subgroup analyses, the association between metabolic phenotypes of obesity and incident CRM multimorbidity was further examined separately among men and women, as well as participants aged <55 and ≥55 years. Furthermore, we performed a series of sensitivity analyses. First, we restricted the duration of the study's follow-up to the first 10 years to mitigate the impact of time-varying confounders, including the impact of aging, on our results. Second, to further address the impact of aging, we repeated our analyses in a subsample of individuals aged 20 to 45 years who did not reach the age of 65 years by the end of the follow-up period. Third, the association between metabolic phenotypes and CRM multimorbidity was reassessed, accounting for the competing risk of cancer and death using the Fine and Gray method. Moreover, some studies did not include hypertension as a cardiometabolic component in their analyses[20,42]; however, some others have considered it.[7,36–40] Therefore, as the fourth sensitivity analysis, we excluded it as a component of CVD in the definition of CRM multimorbidity and adjusted our models for the baseline status of hypertension.

To address the issue of selection and survival bias due to missing data, multiple imputation was performed as a sensitivity analysis under the assumption of missing at random. Under this assumption, nonresponse was considered unrelated to outcomes and fully explained by observed variables. Multivariate imputation using the 2-fold Fully Conditional Specification algorithm, suitable for longitudinal routinely collected clinical data, was used to impute missing data for fixed and time-varying variables.[43,44] This method accounts for the longitudinal structure of the data by restricting imputation of each variable to time blocks, by using only data from a particular time point and the immediately adjacent ones, which prevents issues of collinearity and overfitting.[45–47] The imputation model included all variables in the analysis as well as the outcome and survival time as explanatory variables, as omitting the outcome variable from the imputation model introduces bias.[48] However, because CRM multimorbidity outcome data were missing for a substantial proportion of individuals and since data on CVD events were collected annually (thus being available for ≈91% of the imputation sample), we first imputed 50 data sets using Fully Conditional Specification,[49] allowing imputation of missing CVD outcome data. Then, using CVD as the explanatory outcome variable, we used 2-fold Fully Conditional Specification to generate another 50 imputed data sets (with 20 among-time and 5 within-time iterations) according to multiple imputation procedures, using a time window of 1. For imputing the components of CRM multimorbidity outcome, we imputed the variables necessary to define the components of CRM multimorbidity at the triennial visits (eg,

FPG, 2h-PG, SBP, DBP, serum creatinine, and medications). We excluded individuals who died before attending a subsequent exam after baseline from the imputation sample. Finally, individuals were removed from the imputation models at death.

Thus, we performed analysis (1) excluding observations with missing values on variables in the adjusted model (complete-case analysis, n=6343), and (2) using multiply imputed data (n=8509).

Since the missing-at-random assumption underlying multiple imputation is inherently untestable and may not hold for the outcome, we also performed best–worst and worst–best sensitivity analyses for the outcome, using Poisson regression to estimate risk ratios and 95% CIs, assessing the potential that the missing not at random may have on the estimated results.[50] In 2 additional sensitivity analyses, we assumed that all individuals with unknown outcome status were either entirely free of the outcome or had all developed the outcome.

Figures were created in R (version 4.4.0). All analyses were conducted using STATA version 14 SE (StataCorp LP, College Station, TX), with a 2-tailed *P* value <0.05 considered statistically significant.

RESULTS

Baseline Characteristics

At baseline, 6343 participants (56.05% women) with a mean±SD age of 37.06±11.74 years and BMI of 26.22 (4.28) kg/m^2 were enrolled in the study, including 1219 metabolically healthy and 5124 metabolically unhealthy individuals. Higher BMI was significantly associated with elevated levels of FPG, 2h-PG, SBP, DBP, total cholesterol, and triglycerides, as well as lower eGFR in both metabolically healthy and unhealthy groups. Additionally, being married, having <6 years of education, and having a family history of CVD or diabetes were more prevalent among participants with obesity compared with their normal-weight counterparts in both groups (Table 1).

Comparison of the baseline characteristics between respondents and nonrespondents is provided in Table S1. Compared with respondents, nonrespondents were younger and had lower levels of BMI, WC, SBP, and total cholesterol but higher eGFR. Additionally, being married and a current smoker were more prevalent among respondents and nonrespondents, respectively.

Metabolic Phenotypes and Risk of CRM Multimorbidity

Over a median follow-up of 14.3 (interquartile range, 11.2–16.3) years, 2093, 1073, and 869 events of CVD, CKD, and T2D occurred, respectively; 997 participants developed CRM multimorbidity. Kaplan–Meier estimates demonstrated significant differences in CRM multimorbidity-free survival across metabolic phenotypes (Figure 2). Moreover, the distribution of observed condition combinations among individuals who developed CRM multimorbidity during the follow-up period is presented in Figure S1, comparing definitions that either include or exclude hypertension as a component of CVD, and accordingly, as part of the CRM multimorbidity construct.

Table 2 presents the risk of incident CRM multimorbidity across obesity phenotypes using different criteria. Compared with the MHNW phenotype, participants with MHOW (HR, 2.08 [95% CI, 1.35–3.20]), MHO (HR, 2.04 [95% CI, 1.11–3.75]), MUNW (HR, 2.29 [95% CI, 1.61–3.27]), MUOW (HR, 2.83 [95% CI, 2.01–3.99]), and MUO HR, 5.16 [95% CI, 3.64–7.32]) phenotypes had a significantly higher risk of incident CRM multimorbidity in the fully adjusted model. Additionally, metabolically unhealthy participants with overweight (HR, 1.24 [95% CI, 1.05–1.47]) and obesity (HR, 2.25 [95% CI, 1.87–2.71]) were at a 24% and 125% higher risk of incident CRM multimorbidity compared with their normal-weight counterparts, respectively. Similar results were observed when participants with ≤1 of the metabolic abnormalities were classified as metabolically healthy.

Regarding abdominal obesity, compared with the MHNAO phenotype, participants with MHAO (HR, 1.77 [95% CI, 1.19–2.64]), MUNAO (HR, 1.95 [95% CI, 1.48–2.57]), and MUAO (HR, 3.26 [95% CI, 2.49–4.28]) phenotypes had an elevated risk of incident CRM multimorbidity. Additionally, using the MUNAO phenotype as the reference group, the MUAO phenotype was associated with a 70% higher risk of incident CRM multimorbidity (HR, 1.70 [95% CI, 1.48–1.96]).

As an additional analysis, participants were categorized into obese and nonobese (including both normal and overweight categories) groups based on BMI (<30 and ≥30 kg/m^2), and the associations between obesity phenotypes and incident CRM multimorbidity were reassessed. The results were generally consistent (Table S2).

The cumulative incidence and HRs associated with the increasing number of abnormal metabolic components and incident CRM multimorbidity among metabolically unhealthy individuals are shown in Figure 3 and Figures S2 and S3. Across both WC and BMI categories, increase of abnormal metabolic components was associated with a stepwise increase in the risk of incident CRM multimorbidity. We also assessed the interval between first and second CRM morbidities across 6 metabolic phenotypes. Accordingly, no significant differences were found within healthy or unhealthy groups

Table 1. Baseline Characteristics of Study Participants: Tehran Lipid and Glucose Study 1999 to 2018

Characteristics	Total (n=6343)	Metabolically healthy Normal weight (n=745)	Metabolically healthy Overweight (n=374)	Metabolically healthy Obesity (n=100)	Metabolically unhealthy Normal weight (n=1909)	Metabolically unhealthy Overweight (n=2182)	Metabolically unhealthy Obesity (n=1033)
Continuous variables, mean±SD							
Age, y	37.06±11.74	33.71±12.54	37.72±11.58	38.47±11.06*	34.88±11.99	38.57±11.21	39.93±10.54*
BMI, kg/m^2	26.22±4.28	22.01±1.82	27.13±1.40	32.99±2.92*	22.50±1.73	27.28±1.42	32.93±2.87*
WC, cm	86.10±11.27	75.86±6.79	87.18±8.07	98.10±9.85*	77.99±7.22	89.34±7.29	100.08±8.75*
FPG, mg/dL	88.49±8.92	85.08±6.54	86.52±6.90	86.68±6.93*	87.29±8.79	89.84±9.11	91.22±9.72*
2h-PG, mg/dL	102.27±26.99	90.64±21.61	98.25±25.65	105.04±26.07*	97.25±24.93	106.09±27.33	112.23±28.61*
SBP, mm Hg	111.48±11.18	106.76±9.58	109.19±9.94	112.40±9.33*	109.45±11.64	113.42±10.85	115.27±10.54*
DBP, mm Hg	73.71±8.17	69.72±7.78	72.18±7.15	74.79±6.70*	72.08±8.50	75.13±7.71	77.10±7.14*
Pulse rate, beats/min	78.98±11.31	78.20±11.27	78.69±10.41	79.96±9.95	78.94±11.68	78.76±11.22	80.07±11.21†
eGFR, mL/min per 1.73 m^2	85.26±13.18	88.50±13.10	82.99±11.82	82.09±12.49*	88.20±13.52	83.62±12.70	82.09±12.57*
TC, mg/dL	196.73±42.43	182.03±34.99	198.81±36.98	207.09±35.50*	185.38±40.66	204.08±42.97	210.99±43.37*
HDL-C, mg/dL	41.68±10.88	54.34±9.30	54.66±10.11	57.17±9.03‡	39.04±8.39	37.94±8.54	39.11±9.29*
Triglycerides, median (IQR), mg/dL	126 (87–186)	79 (61–103)	91 (71–114)	102 (78–123)*	113 (83–169)	156 (111–219)	169 (121–229)*
Categorical variables, n (%)							
Sex, female	3555 (56.05)	387 (51.95)	230 (61.50)	75 (75.0)*	964 (50.50)	1185 (54.31)	714 (69.12)*
Married	5054 (79.68)	480 (64.43)	318 (85.03)	81 (81.0)*	1366 (71.56)	1890 (86.62)	919 (88.96)*
Educational level, y							
<6	1380 (21.76)	114 (15.30)	76 (20.32)	28 (28.0)†	304 (15.92)	505 (23.14)	353 (34.17)*
6–12	3947 (62.23)	494 (66.31)	236 (63.10)	64 (64.0)	1237 (64.80)	1335 (61.18)	581 (56.25)
>12	1016 (16.01)	137 (18.39)	62 (16.58)	8 (8.0)	368 (19.28)	342 (15.68)	99 (9.58)
Smoking status							
Never	4886 (77.03)	583 (78.26)	303 (81.02)	81 (81.0)	1407 (73.70)	1662 (76.17)	850 (82.28)*
Former	378 (5.96)	44 (5.91)	25 (6.68)	7 (7.0)	110 (5.76)	135 (6.19)	57 (5.52)
Current	1079 (17.01)	118 (15.84)	46 (12.30)	12 (12.0)	392 (20.54)	385 (17.64)	126 (12.20)
Family history of CVD	911 (14.36)	81 (10.87)	53 (14.17)	21 (21.0)†	251 (13.15)	321 (14.71)	184 (17.81)†
Family history of diabetes	1644 (25.92)	156 (20.94)	94 (25.13)	35 (35.0)†	438 (22.94)	619 (28.37)	302 (29.24)*
Lipid-lowering drug use	63 (0.99)	0 (0.0)	0 (0.0)	0 (0.0)	9 (0.47)	30 (1.37)	24 (2.32)*

2h-PG indicates 2-h postchallenge glucose; BMI, body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; SBP, systolic blood pressure; TC, total cholesterol; and WC, waist circumference.

*P<0.01.

†P<0.01.

‡P<0.05.

with increasing BMI, nor between metabolically healthy and unhealthy phenotypes (Figure S4).

Subgroup Analysis

During the study period, 6.14, 14.58, 16.00, 12.59, 16.65, and 24.76% of men and 3.61, 12.60, 14.66, 9.14, 18.07, and 32.21% of women with MHNW, MHOW, MHO, MUNW, MUOW, and MUO phenotypes, respectively, developed CRM multimorbidity (Table 3).

As shown in Table 3, compared with the MHNW phenotype, other phenotypes—including MHOW, MHO, MUNW, MUOW, and MUO—were associated with incident CRM multimorbidity among men with HRs of 1.77 (95% CI, 0.97–3.23), 3.70 (95% CI, 1.26–10.84), 1.91 (95% CI, 1.21–3.02), 2.33 (95% CI, 1.48–3.64), and 4.50 (95% CI, 2.78–7.28), respectively; the corresponding HRs among women were 2.47 (95% CI, 1.30–4.69), 2.06 (95% CI, 0.93–4.56), 2.79 (95% CI, 1.59–4.91), 3.48 (95% CI, 2.02–5.99), and 6.10 (95% CI, 3.55–10.50), respectively. Using the MUNW phenotype as the reference group, the MUOW and MUO phenotypes were associated with 22% and 132% higher risk of incident CRM multimorbidity among men, as well as 26% and

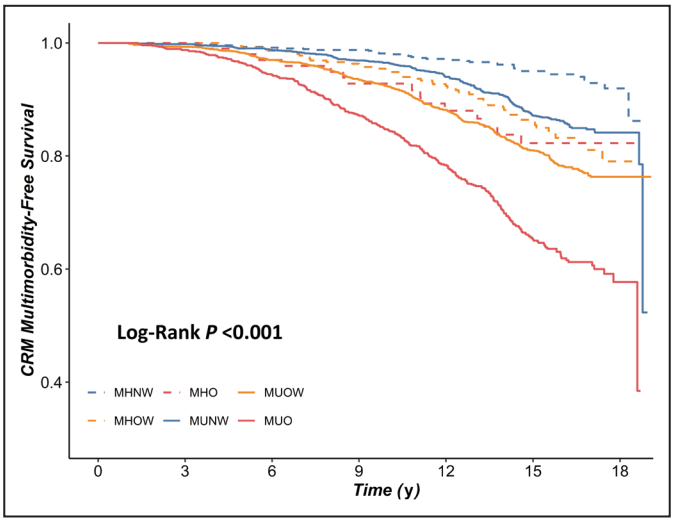

Figure 2. CRM multimorbidity-free survival determination by Kaplan–Meier analysis: Tehran Lipid and Glucose Study 1999 to 2018.

The median follow-up duration was 14.3 y. Participants were classified into 6 groups based on baseline metabolic health and obesity status. A significant difference was observed between groups (log-rank test, *P*<0.001). CRM, cardio–renal–metabolic; MHNW, metabolically healthy normal weight; MHO, metabolically healthy obesity; MHOW, metabolically healthy overweight; MUO, metabolically unhealthy obesity; MUNW, metabolically unhealthy normal weight; and MUOW, metabolically unhealthy overweight.

124% higher risk among women, respectively. Although the effect sizes for different phenotypes were generally higher among women compared with men, no significant interaction was observed (all *P* interactions >0.05).

Table 4 presents the association of different metabolic phenotypes with CRM multimorbidity risk, stratified by age. Among participants aged <55 years, compared with the MHNW group, phenotypes including MHOW, MHO, MUNW, MUOW, and MUO were significantly associated with incident CRM multimorbidity, with HRs of 2.30 (95% CI, 1.31–4.05), 2.43 (95% CI, 1.12–5.24), 2.54 (95% CI, 1.57–4.11), 3.32 (95% CI, 2.08–5.31), and 6.90 (95% CI, 4.30–11.06), respectively; and corresponding values among older participants were 2.23 (95% CI, 1.11–4.45), 1.42 (95% CI, 0.50–4.00), 2.22 (95% CI, 1.29–3.81), 2.22 (95% CI, 1.31–3.75), and 2.63 (95% CI, 1.48–4.67), respectively. Additionally, compared with the MHO, the association between MUO phenotype and risk of incident CRM multimorbidity was more prominent among the younger adults (*P* for interaction=0.014). Moreover, in participants aged <55 years, compared with the MUNW, those with MUOW and MUO phenotypes had a significantly higher risk of incident CRM multimorbidity.

Sensitivity Analyses

We reassessed our main findings across a series of sensitivity analyses. First, the study's follow-up duration was restricted to the first 10 years, and generally similar results were observed (Table S3). Second, the association between obesity phenotypes and CRM multimorbidity was examined among a subsample of younger participants aged between 20 and 45 years, and consistent results were found (Table S4). Third, considering incident cancer and all-cause death as competing risk in our statistical models did not alter our findings (Table S5). Fourth, we excluded hypertension as a component of CVD and repeated the primary analysis among a subsample of 7439 participants. Accordingly, observed results generally remained unchanged (Table S6).

Results of the sensitivity analysis of imputed data are presented in Table S7. Accordingly, the results were largely consistent with those from the complete-case analysis across all models. Notably, the association between the MUOW phenotype and incident CRM multimorbidity, compared with the MUNW reference group, became statistically significant.

Worst–best case sensitivity analyses indicated that if all nonrespondents in the reference group (MHNW) developed the outcome, while all nonrespondents in the comparison groups remained free of CRM multimorbidity, then the MHOW, MHO, MUNW, MUOW, and MUO phenotypes would all have been associated with a significantly lower risk of CRM multimorbidity in the multivariable model (all *P*<0.001). Conversely, if all nonrespondents in the reference group remained free

Table 2. Risk of Incident CRM Multimorbidity for the Different Groups of Metabolic Phenotypes Defined by Different Criteria: Tehran Lipid and Glucose Study 1999 to 2018

Groups	Events/no. at risk	Model 1 HR (95% CI)	*P* value	Model 2 HR (95% CI)	*P* value	Model 3 HR (95% CI)	*P* value
Definition 1							
MHNW	36/745	1.0	…	1.0	…	1.0	…
MHOW	50/374	2.84 (1.85–4.36)	<0.001	2.31 (1.50–3.54)	<0.001	2.08 (1.35–3.20)	0.001
MHO	15/100	3.24 (1.77–5.91)	<0.001	2.38 (1.30–4.35)	0.005	2.04 (1.11–3.75)	0.02
MUNW	207/1909	2.30 (1.61–3.28)	<0.001	2.36 (1.66–3.37)	<0.001	2.29 (1.61–3.27)	<0.001
MUOW	380/2182	3.82 (2.72–5.38)	<0.001	3.13 (2.22–4.40)	<0.001	2.83 (2.01–3.99)	<0.001
MUO	309/1033	7.59 (5.37–10.72)	<0.001	5.77 (4.08–8.16)	<0.001	5.16 (3.64–7.32)	<0.001
Among metabolically unhealthy participants							
MUNW	207/1909	1.0	…	1.0	…	1.0	…
MUOW	380/2182	1.66 (1.40–1.97)	<0.001	1.33 (1.12–1.57)	0.001	1.24 (1.05–1.47)	0.014
MUO	309/1033	3.29 (2.76–3.93)	<0.001	2.43 (2.03–2.92)	<0.001	2.25 (1.87–2.71)	<0.001
Definition 2							
MHNW	125/2002	1.0	…	1.0	…	1.0	…
MHOW	149/1307	1.84 (1.45–2.33)	<0.001	1.46 (1.15–1.85)	0.002	1.33 (1.05–1.69)	0.02
MHO	91/465	3.45 (2.63–4.52)	<0.001	2.33 (1.78–3.07)	<0.001	2.14 (1.63–2.82)	<0.001
MUNW	118/652	2.98 (2.31–3.83)	<0.001	2.13 (1.66–2.75)	<0.001	2.03 (1.57–2.61)	<0.001
MUOW	281/1249	3.91 (3.17–4.83)	<0.001	2.62 (2.12–3.24)	<0.001	2.39 (1.93–2.96)	<0.001
MUO	233/668	7.09 (5.70–8.81)	<0.001	4.71 (3.78–5.87)	<0.001	4.18 (3.34–5-22)	<0.001
Among metabolically unhealthy participants							
MUNW	118/652	1.0	…	1.0	…	1.0	…
MUOW	281/1249	1.31 (1.06–1.63)	0.01	1.20 (0.97–1.49)	0.09	1.16 (0.93–1.44)	0.18
MUO	233/668	2.36 (1.89–2.94)	<0.001	2.09 (1.66–2.63)	<0.001	1.96 (1.55–2.48)	<0.001
Definition 3							
MHNAO	59/965	1.0	…	1.0	…	1.0	…
MHAO	42/254	2.94 (1.98–4.37)	<0.001	1.90 (1.28–2.82)	0.002	1.77 (1.19–2.64)	0.005
MUNAO	364/2999	2.01 (1.52–2.64)	<0.001	1.99 (1.51–2.62)	<0.001	1.95 (1.48–2.57)	<0.001
MUAO	532/2125	4.92 (3.76–6.44)	<0.001	3.51 (2.68–4.60)	<0.001	3.26 (2.49–4.28)	<0.001
Among metabolically unhealthy participants							
MUNAO	364/2999	1.0	…	1.0	…	1.0	…
MUAO	532/2125	2.44 (2.14–2.79)	<0.001	1.78 (1.56–2.05)	<0.001	1.70 (1.48–1.96)	<0.001

Model 1: unadjusted. Model 2: adjusted for age and sex. Model 3: adjusted for model 2 covariates plus smoking status, education level, marital status, pulse rate, eGFR, family history of premature CVD, and family history of diabetes. MHO definition 1 characterized MHO as the absence of any other metabolic abnormalities, including blood pressure, triglycerides, high-density lipoprotein cholesterol, and fasting plasma glucose. MHO definition 2 was similar to MHO definition 1, but participants were only defined as metabolically healthy if they met ≤1 of the aforementioned metabolic abnormalities. MHO definition 3 was similar to MHO definition 1, with obesity defined by waist circumference (≥89 cm in men, ≥91 cm in women) instead of body mass index. CRM indicates, cardio-renal-metabolic; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio; MHAO, metabolically healthy abdominal obesity; MHNAO, metabolically healthy nonabdominal obesity; MHNW, metabolically healthy normal weight; MHO, metabolically healthy obesity; MHOW, metabolically healthy overweight; MUAO, metabolically unhealthy abdominal obesity; MUNW, metabolically unhealthy normal weight; MUO, metabolically unhealthy obesity; MUNAO, metabolically unhealthy nonabdominal obesity; and MUOW, metabolically unhealthy overweight.

of CRM multimorbidity and all nonrespondents in the comparison groups developed the outcome, the results would have been associated with a higher risk of CRM multimorbidity. Findings in line with those of our complete-case analyses were observed across most metabolic obesity phenotype groups when assuming that all individuals with unknown outcome status were either entirely free of the outcome or had all developed CRM multimorbidity (Table S8).

DISCUSSION

In this population-based, prospective cohort study with nearly 2 decades of follow-up, we report 3 main findings:

1. Regarding general obesity, compared with the MHNW phenotype, all other phenotypes (including MHOW) were associated with >2-fold higher

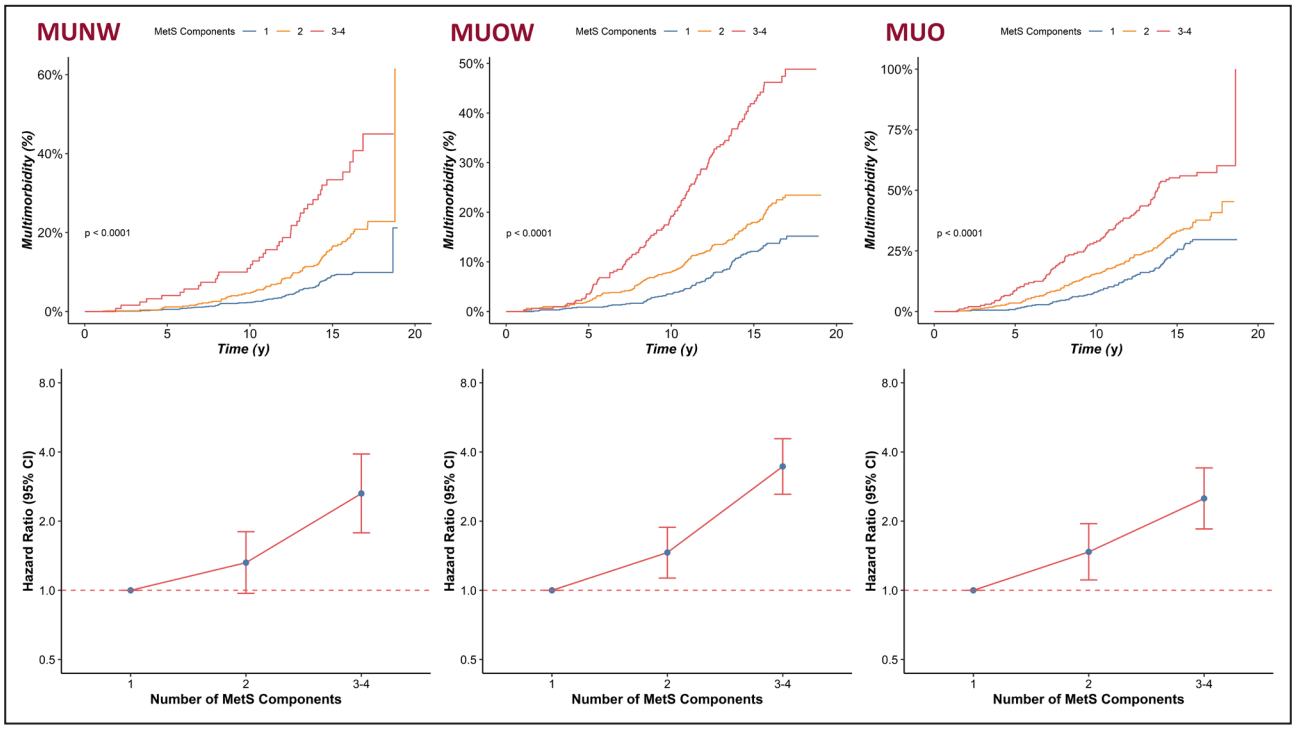

Figure 3. Association of increasing number of abnormal metabolic components with incident CRM multimorbidity among individuals with metabolically unhealthy phenotypes: Tehran Lipid and Glucose Study 1999 to 2018.
CRM indicates cardio–renal–metabolic; MetS, metabolic syndrome; MUNW, metabolically unhealthy normal weight; MUO, metabolically unhealthy obesity; and MUOW, metabolically unhealthy overweight.

risk of incident CRM multimorbidity. Among individuals with an unhealthy phenotype, higher weight was linked to an increased risk of CRM multimorbidity.

2. Regarding abdominal obesity, compared with the MHNAO phenotype, the risk of incident CRM multimorbidity was approximately 77%, 95%, and 226% higher among participants with MHAO, MUNAO, and MUAO phenotypes, respectively.
3. We observed indications of stronger associations between metabolic phenotypes and incident CRM multimorbidity among women and younger individuals.

Due to the lack of a universally accepted definition for MHO, >30 distinct definitions have been used across studies, resulting in significant inconsistencies in the literature.[51,52] Additionally, variations in follow-up periods across studies represent another potential source of discrepancy.[53,54] Aligned with the transient nature of metabolic phenotypes,[55] the gradual progression of NCDs over a person's life span suggests that studies with shorter follow-up durations may underestimate the impact of obesity on an individual's health.

In recent years, numerous researchers have attempted to elucidate the risk of incident major NCDs, including diabetes,[56,57] hypertension,[58] CKD,[24] and CVD[25] on the basis of obesity and metabolic status. However, evidence has shown inconsistent results regarding certain metabolic phenotypes of obesity, particularly MHOW, MHO, and MUNW.[53,59] While the detrimental role of adipose tissue in the development of major NCDs is widely recognized,[60] some studies have suggested that maintaining normal weight does not necessarily ensure metabolic health.[23] In our study, more than two thirds of the 2654 participants with normal weight had a metabolically unhealthy condition, associated with a >2-fold increased risk of incident multimorbidity compared with their metabolically healthy counterparts. In contrast, our previous study found that the association between the MUNW phenotype and incident hypertension was significant only among women.[29] Recent systematic reviews and meta-analyses have similarly shown that individuals with the MUNW phenotype are at an elevated risk of major NCDs, including CKD,[24] CVD,[25] diabetes,[27] and hypertension,[28] compared with those with the MHNW phenotype. Additionally, from a biological perspective, the increased risk of NCDs among individuals with the MUNW phenotype is primarily attributed to insulin disturbances.[23]

Regarding phenotypes with overweight and obesity, while some studies have suggested these as benign conditions in the absence of metabolic abnormalities,[54] recent meta-analyses and cohort studies

Table 3. Sex-Stratified Risk of Incident CRM Multimorbidity Across Different Metabolic Phenotypes: Tehran Lipid and Glucose Study 1999 to 2018

Groups	Events/no. at risk	Model 1 HR (95% CI)	*P* value	Model 2 HR (95% CI)	*P* value	Model 3 HR (95% CI)	*P* value
Men							
MHNW	22/358	1.0	…	1.0	…	1.0	…
MHOW	21/144	2.29 (1.26–4.17)	0.007	1.94 (1.07–3.53)	0.03	1.77 (0.97–3.23)	0.06
MHO	4/25	3.17 (1.09–9.19)	0.03	3.90 (1.34–11.32)	0.01	3.70 (1.26–10.84)	0.02
MUNW	119/945	2.08 (1.32–3.28)	0.002	2.02 (1.28–3.19)	0.002	1.91 (1.21–3.02)	0.005
MUOW	166/997	2.81 (1.80–4.38)	<0.001	2.58 (1.65–4.03)	<0.001	2.33 (1.48–3.64)	<0.001
MUO	79/319	4.91 (3.06–7.87)	<0.001	4.84 (3.01–7.77)	<0.001	4.50 (2.78–7.28)	<0.001
Among metabolically unhealthy participants							
MUNW	119/945	1.0	…	1.0	…	1.0	…
MUOW	166/997	1.34 (1.06–1.70)	0.01	1.28 (1.01–1.62)	0.04	1.22 (0.96–1.54)	0.11
MUO	79/319	2.34 (1.76–3.11)	<0.001	2.38 (1.79–3.16)	<0.001	2.32 (1.73–3.12)	<0.001
Women							
MHNW	14/387	1.0	…	1.0	…	1.0	…
MHOW	29/230	3.73 (1.97–7.07)	<0.001	2.82 (1.49–5.33)	0.001	2.47 (1.30–4.69)	0.006
MHO	11/75	4.11 (1.87–9.06)	<0.001	2.39 (1.09–5.28)	0.03	2.06 (0.93–4.56)	0.08
MUNW	88/964	2.60 (1.48–4.57)	0.001	2.90 (1.65–5.09)	<0.001	2.79 (1.59–4.91)	<0.001
MUOW	214/1185	5.41 (3.15–9.30)	<0.001	3.79 (2.21–6.52)	<0.001	3.48 (2.02–5.99)	<0.001
MUO	230/714	11.06 (6.45–18.97)	<0.001	6.86 (4.00–11.77)	<0.001	6.10 (3.55–10.50)	<0.001
Among metabolically unhealthy participants							
MUNW	88/964	1.0	…	1.0	…	1.0	…
MUOW	214/1185	2.08 (1.63–2.67)	<0.001	1.33 (1.03–1.71)	0.02	1.26 (0.98–1.63)	0.06
MUO	230/714	4.26 (3.33–5.44)	<0.001	2.41 (1.87–3.09)	<0.001	2.24 (1.73–2.88)	<0.001

Model 1: unadjusted. Model 2: adjusted for age. Model 3: adjusted for model 2 covariate plus smoking status, education level, marital status, pulse rate, eGFR, family history of premature CVD, and family history of diabetes. MHO was defined as the absence of any other metabolic abnormalities including blood pressure, triglycerides, high-density lipoprotein cholesterol, and fasting plasma glucose. CI indicates confidence intervals; CRM, cardio–renal–metabolic; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio; MHAO, metabolically healthy abdominal obesity; MHNAO, metabolically healthy nonabdominal obesity; MHNW, metabolically healthy normal weight; MHO, metabolically healthy obesity; MHOW, metabolically healthy overweight; MUAO, metabolically unhealthy abdominal obesity; MUNW, metabolically unhealthy normal weight; MUO, metabolically unhealthy obesity; MUNAO, metabolically unhealthy nonabdominal obesity; and MUOW, metabolically unhealthy overweight. All multivariable adjusted *P* interaction for sex and metabolic phenotypes >0.05.

involving large populations and extended follow-up periods have refuted this concept.[24–26,61] Notably, our findings indicated that elevated body weight, even within the overweight range, is associated with a higher risk of incident CRM multimorbidity regardless of metabolic status. This aligns with our previous study, which found that being healthy overweight, and obese was associated with a 76% and 41% increased risk of CVD events, respectively[62]; however, these associations did not reach statistical significance, primarily due to insufficient statistical power. In addition, systematic reviews and meta-analyses have shown that, compared with the MHNW phenotype, having MHOW and MHO phenotypes are associated with a 30% and 60% increased risk of CVD, as well as an 18% and 54% increased risk of hypertension, respectively.[25,28] Similarly, a systematic review and meta-analysis of 6 studies reported that being overweight and obese among metabolically healthy individuals was associated with a 19% and 114% increased risk of incident diabetes, respectively.[27] Another systematic review and meta-analysis involving 5 million participants demonstrated that the MHO phenotype is associated with an ≈40% increased risk of incident CKD.[24] Consistent with recent meta-analyses on CKD,[24] T2D,[27] and hypertension,[28] we observed an increased risk among subjects with obesity without any metabolic abnormalities, which was approximately equivalent to that of the MUNW phenotype.

Furthermore, the vast majority of previous studies did not define obesity status on the basis of abdominal obesity, which was associated with a nearly 77% higher risk of CRM multimorbidity, even in the absence of metabolic abnormalities in our study. Similarly, in previous studies, we demonstrated that among metabolically healthy individuals (defined as having <2 abnormal metabolic components), abdominal obesity was associated with incident CVD and diabetes.[63,64] Additionally, a prospective study involving 4764

Table 4. Age-Stratified Risk of Incident CRM Multimorbidity Across Different Metabolic Phenotypes: Tehran Lipid and Glucose Study 1999 to 2018

Groups	Events/no. at risk	Model 1 HR (95% CI)	*P* value	Model 2 HR (95% CI)	*P* value	Model 3 HR (95% CI)	*P* value
<55 y							
MHNW	19/680	1.0	…	1.0	…	1.0	…
MHOW	34/342	3.65 (2.08–6.40)	<0.001	2.45 (1.40–4.31)	0.002	2.30 (1.31–4.05)	0.004
MHO	10/91	4.17 (1.94–8.98)	<0.001	2.68 (1.24–5.78)	0.01	2.43 (1.12–5.24)	0.02
MUNW	138/1753	2.89 (1.79–4.67)	<0.001	2.56 (1.58–4.13)	<0.001	2.54 (1.57–4.11)	<0.001
MUOW	273/1973	5.23 (3.29–8.33)	<0.001	3.53 (2.22–5.64)	<0.001	3.32 (2.08–5.31)	<0.001
MUO	257/929	12.23 (7.68–19.50)	<0.001	7.49 (4.68–11.98)	<0.001	6.90 (4.30–11.06)*	<0.001
Among metabolically unhealthy participants							
MUNW	138/1753	1.0	…	1.0	…	1.0	…
MUOW	273/1973	1.81 (1.47–2.22)	<0.001	1.39 (1.13–1.71)	0.002	1.32 (1.07–1.62)	0.009
MUO	257/929	4.22 (3.43–5.19)	<0.001	2.93 (2.36–3.63)	<0.001	2.73 (2.20–3.39)	<0.001
≥55 y							
MHNW	17/65	1.0	…	1.0	…	1.0	…
MHOW	16/32	2.12 (1.07–4.20)	0.03	2.26 (1.14–4.48)	0.02	2.23 (1.11–4.45)	0.02
MHO	5/9	1.95 (0.72–5.29)	0.19	1.78 (0.65–4.88)	0.26	1.42 (0.50–4.00)	0.51
MUNW	69/156	1.80 (1.06–3.07)	0.03	2.16 (1.26–3.70)	0.005	2.22 (1.29–3.81)	0.004
MUOW	107/209	2.27 (1.36–3.80)	0.002	2.40 (1.43–4.03)	0.001	2.22 (1.31–3.75)	0.003
MUO	52/104	2.33 (1.34–4.04)	0.003	2.53 (1.44–4.45)	0.001	2.63 (1.48–4.67)*	0.001
Among metabolically unhealthy participants							
MUNW	69/156	1.0	…	1.0	…	1.0	…
MUOW	107/209	1.25 (0.92–1.69)	0.15	1.10 (0.81–1.51)	0.53	0.97 (0.71–1.34)	0.87
MUO	52/104	1.28 (0.89–1.84)	0.18	1.18 (0.80–1.73)	0.41	1.16 (0.78–1.73)	0.45

Model 1: unadjusted. Model 2: adjusted for age and sex. Model 3: adjusted for model 2 covariate plus smoking status, education level, marital status, pulse rate, eGFR, family history of premature CVD, and family history of diabetes. MHO was defined as the absence of any other metabolic abnormalities, including blood pressure, triglycerides, high-density lipoprotein cholesterol, and fasting plasma glucose. CRM indicates cardio–renal–metabolic; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio; MHAO, metabolically healthy abdominal obesity; MHNAO, metabolically healthy nonabdominal obesity; MHNW, metabolically healthy normal weight; MHO, metabolically healthy obesity; MHOW, metabolically healthy overweight; MUAO, metabolically unhealthy abdominal obesity; MUNW, metabolically unhealthy normal weight; MUO, metabolically unhealthy obesity; MUNAO, metabolically unhealthy nonabdominal obesity; and MUOW, metabolically unhealthy overweight.

*Compared with the MHO, the association between MUO phenotype and risk of incident CRM multimorbidity was more prominent among the younger adults (*P* for interaction=0.014).

Chinese participants found that, compared with individuals with the MHNAO phenotype (defined as WC <90 cm in men and <80 cm in women and <2 metabolic abnormalities), the risk of developing prehypertension and hypertension was increased by ≈90% and 160%, respectively, among those with abdominal obesity.[58]

Our results were consistent across men and women, with no significant effect modification by sex. Similar to our data analysis, another systematic review and meta-analysis indicated that, compared with the MHNW phenotype, the MHO phenotype was associated with a higher risk of incident CVD among women (115%) rather than men (71%) without significant interaction.[25] Of note, we observed a signal suggesting stronger associations between unhealthy metabolic phenotypes and the development of multimorbidity among younger adults. This finding underscores the importance of weight management and primary prevention in young and middle-aged individuals. In accordance with this finding, the significant role of non–high-density lipoprotein cholesterol and BMI in the development of CVD, as well as BMI for the prediction of diabetes among younger compared with older individuals, has also been highlighted in recent meta-analyses.[65–67]

If missingness in CRM multimorbidity outcome was not random, then multiple imputation would have partially corrected for bias under the missing-not-at-random scenario.[68] Our worst–best sensitivity analyses showed what the results would be like under some extreme scenarios. Assuming nonresponse to be more common among individuals with poorer health outcomes, we performed a sensitivity analysis classifying all participants with missing outcome data as having developed CRM multimorbidity; the majority of the associations remained in line with those from the complete-case analyses. Furthermore, in our study,

compared with respondents, nonrespondents were younger and had lower BMI, WC, SBP, and total cholesterol as well as higher eGFR levels. Another sensitivity analysis, in which all participants with missing outcome data were classified as remaining free from CRM multimorbidity, yielded results for all comparison groups that remained statistically significant and consistent with the main analyses.

The findings of the current study should be interpreted with caution due to several limitations. First, our results may not be generalizable to rural areas. Second, to our knowledge, there is no prespecified definition regarding multimorbidity; and we defined CRM multimorbidity using 3 major NCDs including CVD, CKD, and T2D. Therefore, our results may not be extrapolatable to other NCDs. Third, another limitation is survival bias, and due to loss to follow-up, it is possible that the associations observed in the current study were partly under- or overestimated. Fourth, our study determined CKD on the basis of eGFR values, as data on participants' albumin-to-creatinine ratio were unavailable. Finally, the exact date of onset was available only for CVD, and since the accurate onset time of T2D, CKD, and hypertension was unavailable, we approximated the onset time using the midpoint imputation method. Although this approach has been adopted in many studies,[69–74] the exact timing could not be fully guaranteed, and some measurement error might have been introduced. To partially address this, we imputed missing data across follow-up exams conducted every 3 years to yield narrow and consistent intervals for ascertaining these conditions.

Despite these limitations, this study has several notable strengths. To the best of our knowledge, it is the first study to evaluate the association between metabolic phenotypes of both abdominal and general obesity and incident CRM multimorbidity. Additionally, NCD events in our study were determined through adjudication by an outcome committee rather than relying on self-reported data. Furthermore, while the varying definitions of a metabolically healthy condition have been a significant source of heterogeneity among studies—and most previous studies have defined metabolic health as having <2 abnormal metabolic components—we had the statistical power to define metabolically healthy phenotypes as the absence of any metabolic abnormalities.

In conclusion, our findings suggest that a BMI exceeding 25 kg/m^2 is associated with an increased risk of CRM multimorbidity, even in the absence of metabolic abnormalities. These results indicate that no benign phenotype of elevated body weight exists beyond normal weight. Therefore, maintaining a normal weight, without any metabolic syndrome components, may be essential for preventing the development of CRM multimorbidity.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S8
Figures S1–S4

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