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RESEARCH ARTICLE

Exploring metabolically healthy obesity: prevalence, characteristics, and cardiovascular risk in the Iranian population based on the STEPS 2021

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Abstract

Background Regarding the rapidly increasing prevalence of obesity throughout the globe, it remains a serious public health concern. A subgroup of obesity that does not meet metabolic syndrome criteria is called metabolically healthy obesity (MHO). However, whether the MHO phenotype increases cardiovascular disease (CVD) risk is controversial. This study aimed to evaluate the prevalence of MHO and its 10-year CVD risk in Iranian populations.

Methods Based on the STEPS 2021 project in Iran, we collected data on 18119 Iranians 25 years and older from all 31 provinces after applying many statistical factors. Using the Framingham score, we evaluated the 10-year cardiovascular risk associated with the various MHO definition criteria for Iranian populations.

Results The prevalence of MHO was 6.42% (5.93—6.91) at the national level according to the AHA-NHLBI definition, and 23.29% of obese women and 24.55% of obese men were classified as MHOs. Moreover, the MHO group was younger than the metabolically unhealthy obesity (MUO) group based on all definitions ($p < 0.001$). The odds ratio of MUO individuals being classified as high-risk individuals by the Framingham criteria for CVD was significantly higher than that of MHO individuals by all definitions, with a crude odds ratio of 3.55:1 based on AHA-NHLBI definition.

Conclusion This study reveals a significant prevalence of MHO in the Iranian population, with approximately 25% of obese individuals classified as MHO. While MHO is associated with a lower risk of cardiovascular disease compared to MUO, MHO carries the potential for transitioning to an unhealthy state.

Keywords Cardiovascular diseases · Metabolic syndrome · Obesity · Public health · World Health Organization

Introduction

The prevalence of obesity is rapidly increasing worldwide, posing a significant public health concern [1]. The World Health Organization (WHO) estimates that 1.9 billion individuals are overweight or obese, with 650 million of whom are classified as obese [1]. This trend is observed in both developed and developing countries [2, 3]. The Iranian population's recent adoption of sedentary lifestyles and rapid westernization of nutrition habits may led to the recent increase in overweight and obesity [4]. A review study performed in Iran found that 24.1% of adults over the age of 50 are obese [5]. Obesity has been shown to be a predisposing factor for a variety of physical and psychological comorbidities, including cardiovascular disease (CVD), type 2 diabetes mellitus, sleep apnea, hypertension, specific cancers, hyperlipidemia, non-alcoholic fatty liver, and gall bladder disease, depression, and anxiety [6–9]. CVD is the leading cause of mortality among obese persons [10]. Since obesity has become a global epidemic, it has led to enormous financial burdens on healthcare systems. Obesity is

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estimated to be responsible for 0.7% to 2.8% of the total country's medical costs [11].

Metabolically healthy obesity (MHO) is a new term that refers to a subgroup of individuals who are obese (BMI ≥ 30 kg/m) but do not meet metabolic syndrome criteria [12]. However, there is currently no consensus on the precise definition of MHO. In the majority of studies, MHO is described as obese individuals who have two or more of the metabolic syndrome criteria, including hypertension, high plasma triglycerides, low plasma HDL, high fast blood sugar, and a large waist circumference [13]. MHO prevalence estimates vary from 10 to 51% across the countries according to Rey-López et al.'s systematic review using ATP III, IDF, and the homeostasis model of assessment of insulin resistance (HOMA-IR) [14]. It is important to note that MHO is not a benign condition and has been associated with a variety of serious chronic diseases like CVD, high blood pressure, type 2 diabetes, chronic kidney disease, and certain kinds of cancer and has the potential to progress into an unhealthy state [15]. However, the association between the MHO phenotype and the risk of CVD remains a topic of controversy [12]. In this regard, several investigations have shown that MHO participants do not have an elevated risk of CVD as compared to unhealthy metabolically obese individuals [16, 17]. For instance, results of a 15.9-year follow-up study conducted by Farhad H et al., showed that CVD events did not increase among MHO phenotypes [18]. On the other hand, some investigations have shown that MHO persons are more likely to develop CVD events and die than metabolically healthy normal-weight (MHNW) adults [19–21]. Hinnouho G et al. performed a 17-year follow-up cohort study and discovered that both the MHO and MUO phenotypes had an increased risk for CVD [21]. These contradictory findings are due to differences in MHO definitions, follow-up period, research methodologies, and the population for whom the study was designed [22].

Accordingly, the purpose of this study was to assess the prevalence of MHO among Iranian populations using different metabolic syndrome criteria and the 10-year risk of developing CVD among these individuals using Framingham risk models.

Method and materials

Study overview and design

This study uses STEPwise approach of WHO to surveillance (STEPS). STEPS is a standardized and unified monitoring system implemented by WHO that enables participating nations to gather, evaluate, and disseminate crucial health data [23]. This survey was cross-sectional research conducted at the national scale in all provinces of Iran.

Study population

This study utilized individual data from the STEPS 2021 project. Candidates were selected using a cluster random selection method to be representative of Iranians 18 years and older from all 31 provinces in Iran, based on both urban and rural locations. The included population was evaluated for demographics, metabolic, and behavioral risk factors using questionnaires, anthropometry, and laboratory tests. People with mental disorders who may not be able to answer the questionnaires, people with physical limitations that prevent anthropometry measurement, pregnant women, and those unable to provide laboratory samples were excluded from the study. Participants provided informed consent and agreed to participate in the study. For STEPS 2021, Iranians aged 18 or older who lived in Iran at the time of data collection were eligible to participate. Consequently, 3176 data collection clusters were created. After applying many statistical factors, 28821 persons were included in the data collection. There were 947 people who declined the survey or were unable to be enlisted. In accordance with the WHO STEPwise approach to risk factor surveillance, sampling and examination processes were conducted by trained experts. Using the latest standard version of the WHO questionnaire (version 3.2), 27,874 participants completed the questionnaire (step 1). In accordance with WHO criteria, trained healthcare experts measured the height, weight, waist circumference, hip circumference, blood pressure, and pulse rate of 27,745 participants (step 2). To target NCDs' risk factors through biochemical blood and urine tests, laboratory measurements were taken on participants aged 25 years or older, a total of 18,119 individuals (step 3). The complete report of Iran STEPS 2021 provides detailed information about the survey [24].

Variables

To define MHO, we used metabolic syndrome criteria, including blood pressure, lipids (mostly HDL and triglycerides), glycemia (fasting blood sugar), and other biological data like waist circumference. Supplementary Table 1 presents details on the seven criteria used to define MHO: National Cholesterol Education Adult Treatment Panel III (ATP III) [25], the International Diabetes Federation (IDF) [26], the American Heart Association/National Heart, Lung, and Blood Institute (AHA-NHLBI) [27], the Joint Interim Statement (JIS) [28], Meigs [29], Regional IDF and Regional JIS [30]. Iran's National Committee on obesity recommended that ethnicity-specific values be applied to the IDF and JIS definitions of obesity which

have separate cutoffs for waist circumference (WC) called Regional IDF and Regional JIS, respectively [30].

The data of variables used to estimate the cardiovascular risk associated with each definition. We evaluated the demographic and clinical parameters by seven criteria. In the laboratory, serum total cholesterol, high-density lipoprotein cholesterol (HDL-C), triglycerides, creatinine, alanine transaminase (ALT), blood urea nitrogen (BUN), whole blood HbA1c, fasting plasma glucose, and urine sodium, potassium, and creatinine were measured using an autoanalyzer (Roche-Hitachi Cobas C311, High–Technologies Corporation, Tokyo, Japan) approved by the reference laboratory [24]. Overweight is considered as a $25 \leq BMI < 30$ kg/m2; Obesity is defined as a $BMI \geq 30$ kg/m2; hypertension is described as a systolic blood pressure of 140 mmHg and/or a diastolic blood pressure of 90 mmHg; and increased blood glucose/diabetes is characterized as a fasting blood sugar of 126 mg/dl OR a HbA1c of 6.5 percent. Age, sex, local residency, province, family history of diabetes, and variables were also included. The estimated glomerular filtration rate (eGFR) was calculated using patients' age, sex, and serum creatinine. We measured urine albumin using Prestige premium 24i.

We assessed the 10-year cardiovascular risk associated with MHO, metabolically unhealthy obesity (MUO), and metabolically healthy non-obese (MHNW) individuals based on various metabolic syndrome criteria using the Framingham score. The Framingham Risk Score, provided by the American Heart Association and the American College of Cardiology, is a widely used multifactor system that estimates an individual's likelihood of experiencing a cardiovascular event, such as a heart attack or stroke, within the next 10 years, considering variables including age, sex, total cholesterol, HDL, systolic blood pressure, and smoking habits. Based on the Framingham Score, high cardiovascular risk is considered to be greater than or equal to 20% [31, 32].

Statistical analysis

In the present study, we estimated the prevalence of MHO in 6 age groups, 25–34, 35–44, 45–54, 55–64, 65–74, and ≥ 75 among all definitions. After finalizing the survey data, variables and outcomes for MHO were defined using the above criteria. In this descriptive analysis, the frequency of MHO prevalence was reported, along with the respective 95% CI or p-value. To compare districts, CI was employed as it suggests a non-significant difference in a variable. Furthurmore, we used model's odds ratios (OR) and 95% confidence intervals (CI). The response variables were reported in binary form, using a logistic regression model. For reporting the results of the analysis, we established a reference category and then compared a second category to the reference. The model was adjusted for age, physical activity, area, school years, wealth index, and current cigarette smoking. We used logistic regression models to estimate crude and adjusted ORs and stratified the results by BMI categories and health status to study associations between metabolic health status and high cardiovascular risk (Framingham score ≥ 20%). Within each BMI category, we considered the metabolically healthy group to be the reference group. All statistical analyses were performed with the STATA software version 14 (STATA Corp., College Station, Texas, USA) and R statistical package for Windows version 4.1.2 (https://cran.r-project.org). Two-tailed P values of 0.05 were considered statistically significant.

Ethical consideration

The ethical committee of the Tehran University of Medical Sciences approved this study under code IR.TUMS.NIHR.REC.1398.006. All authors protect the data of recruited participants. No individual data is reported; results are based only on statistical modeling. Participants provided informed consent in the original survey, Iran STEPS 2021.

Results

A total of 18,119 volunteers participated in the STEPS study 2021, with 10,293 (56.80%) females and 7,826 (43.20%) males aged over 25 years completing the questionnaires and laboratory tests.

Prevalence

Among obese individuals, 23.29% of women and 24.55% of men met the criteria for MHO based on the AHA-NHLBI definition. At the national level, the RIDF definition yielded the highest prevalence of MHO in both sexes with 7.93% (7.35—8.51), whereas the JIS definition yielded the lowest prevalence with 6.22% (5.73—6.71). (Supplementary Table 3) However, based on AHA-NHLBI criteria, the prevalence of MUO was 14.45% (13.72–15.18) for women and 6.24% (5.71–6.77) for men. In all criteria, MUO is more prevalent in women than in men. (Table 1).

The highest prevalence of MHO within AHA-NHLBI criteria among both sexes across the provinces was in Bushehr province which was 8.98% (6.46—11.51), whereas the lowest prevalence was in Sistan and Baluchistan within all definitions (3.56% (1.97—5.15) in AHA-NHLBI). Based on the definition of AHA-NHLBI, the prevalence of MHO is mostly concentrated in Bushehr province, West Azerbaijan province, Ilam, Kurdistan, Khuzestan, Kohgiluyeh and Boyer-Ahmad, Zanjan, and Kermanshah, all located in western Iran. (Supplementary Table 3).

Table 1 Prevalence of obesity phenotype based on different criteria divided by sex

Obesity phenotype	AHA-NHLBI[3]	ATP III[4]	JIS[5]	RJIS[6]	IDF[7]	RIDF[8]	Meigs
BMI < 25, Healthy, Male	14.06 (13.37–14.76)	14.53 (13.82–15.23)	11.94 (11.31–12.58)	13.35 (12.67–14.03)	15.56 (14.84–16.28)	15.9 (15.16–16.64)	14.44 (13.74–15.14)
BMI < 25, Healthy, Female	10.84 (10.23–11.46)	11.19 (10.57–11.82)	11.3 (10.67–11.93)	11.68 (11.04–12.32)	10.05 (9.45–10.65)	13.83 (13.14–14.52)	11.08 (10.46–11.71)
BMI < 25, Unhealthy, Male	3.86 (3.43–4.29)	3.39 (2.98–3.81)	5.98 (5.45–6.5)	4.57 (4.11–5.03)	2.36 (1.99–2.74)	2.02 (1.69–2.35)	3.48 (3.07–3.89)
BMI < 25, Unhealthy, Female	4.26 (3.84–4.68)	3.91 (3.5–4.32)	3.8 (3.4–4.2)	3.42 (3.03–3.81)	5.06 (4.6–5.51)	1.27 (1.03–1.52)	4.02 (3.6–4.44)
25 < = BMI < 30, Healthy, Male	9.21 (8.61–9.81)	9.95 (9.33–10.56)	5.85 (5.35–6.34)	7.09 (6.55–7.62)	8.36 (7.78–8.95)	8.94 (8.34–9.53)	9.65 (9.04–10.26)
25 < = BMI < 30, Healthy, Female	9.85 (9.18–10.53)	10.67 (9.98–11.36)	10.67 (9.98–11.36)	11.7 (10.98–12.42)	8.64 (8.03–9.25)	14.55 (13.78–15.32)	10.39 (9.7–11.07)
25 < = BMI < 30, Unhealthy, Male	9 (8.38–9.63)	8.26 (7.65–8.87)	12.36 (11.66–13.07)	11.12 (10.44–11.8)	9.85 (9.21–10.49)	9.27 (8.64–9.9)	8.56 (7.94–9.18)
25 < = BMI < 30, Unhealthy, Female	11.81 (11.17–12.44)	10.99 (10.37–11.61)	10.99 (10.37–11.6)	9.96 (9.38–10.53)	13.02 (12.32–13.71)	7.11 (6.62–7.6)	11.27 (10.65–11.9)
30 < = BMI, Healthy, Male (MHO[1])	2.03 (1.72–2.34)	2.29 (1.95–2.62)	1.63 (1.35–1.92)	1.75 (1.45–2.04)	1.99 (1.66–2.32)	2.01 (1.68–2.34)	2.16 (1.83–2.48)
30 < = BMI, Healthy, Female (MHO)	4.39 (4–4.77)	4.97 (4.56–5.37)	4.58 (4.18–4.99)	4.95 (4.52–5.38)	4.34 (3.96–4.73)	5.92 (5.43–6.41)	4.72 (4.32–5.12)
30 < = BMI, Unhealthy, Male (MUO[2])	6.24 (5.71–6.77)	5.98 (5.46–6.5)	6.63 (6.09–7.18)	6.52 (5.99–7.06)	6.28 (5.76–6.79)	6.26 (5.74–6.78)	6.11 (5.59–6.63)
30 < = BMI, Unhealthy, Female (MUO)	14.45 (13.72–15.18)	13.87 (13.15–14.59)	14.25 (13.53–14.97)	13.88 (13.17–14.59)	14.49 (13.76–15.22)	12.92 (12.24–13.59)	14.12 (13.39–14.84)

[1]Metabolically healthy obesity

[2]Metabolically unhealthy obesity

[3]American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI)

[4]Adult Treatment Panel III (ATP III)

[5]Joint Interim Statement (JIS)

[6]Regional JIS (RJIS)

[7]International Diabetes Federation (IDF)

[8]Regional IDF

Table 2 Prevalence of obesity and prevalence of MHO by different criteria based on age groups

Age group	Prevalence of obesity (BMI > =30)	AHA-NHLBI[1]	ATP III[2]	JIS[3]	RJIS[4]	IDF[5]	RIDF[6]	Meigs
25–34	17.08 (15.18–18.98)	6.66 (5.63–7.68)	6.88 (5.84–7.93)	6.18 (5.21–7.15)	6.76 (5.75–7.77)	6.41 (5.4–7.41)	7.39 (6.32–8.46)	6.73 (5.7–7.76)
35–44	27.04 (25.21–28.87)	8.33 (7.2–9.45)	8.6 (7.46–9.74)	8.42 (7.24–9.6)	9.17 (7.88–10.45)	8.19 (7.06–9.31)	10.07 (8.75–11.39)	8.48 (7.35–9.62)
45–54	32.74 (30.79–34.69)	7.82 (6.61–9.04)	8.51 (7.26–9.77)	7.57 (6.37–8.77)	8.07 (6.85–9.3)	7.66 (6.46–8.87)	9.53 (8.21–10.86)	8.21 (6.98–9.44)
55–64	31.07 (28.95–33.2)	3.87 (3.12–4.62)	5.47 (4.57–6.37)	3.71 (2.98–4.44)	4.01 (3.23–4.78)	4.25 (3.25–5.24)	5.76 (4.64–6.89)	4.77 (3.93–5.61)
65–74	29 (26.08–31.91)	4.2 (2.85–5.56)	6.43 (4.72–8.14)	3.9 (2.54–5.25)	4.04 (2.66–5.41)	4.1 (2.75–5.44)	6.13 (4.09–8.17)	5.6 (3.98–7.23)
> =75	25.03 (18.69–31.37)	3.7 (1.79–5.61)	4.63 (2.58–6.68)	3.54 (1.63–5.44)	3.54 (1.63–5.44)	3.28 (1.43–5.13)	3.88 (1.94–5.81)	3.85 (1.93–5.77)

[1]American Heart Association/National Heart, Lung, and Blood Institute (AHA-NHLBI)
[2]Adult Treatment Panel III (ATP III)
[3]Joint Interim Statement (JIS)
[4]Regional JIS (RJIS)
[5]International Diabetes Federation (IDF)
[6]Regional IDF

Within almost all definitions, Alborz province had the highest prevalence of MHO among males (8.09% (0.19—15.99) in JIS). However, the lowest male prevalence of MHO was in Ardebil over approximately all definitions (1.75% (0.08—3.41) in AHA-NHLBI). (Supplementary Table 5) Furthermore, the highest prevalence of MHO among females was found in the west Azerbaijan province across most definitions (e.g., 11.48% (7.49—15.48) in AHA-NHLBI), while almost all criteria showed Yazd province to have the lowest prevalence of MHO among females (2.8% (0.21—5.4) in AHA-NHLBI). (Supplementary Table 4) The prevalence of MHO in both sexes combined for the RIDF definition exhibited the most fluctuation among 31 provinces (range: 4.46%—10.7%). (Supplementary Table 3).

In terms of the prevalence of MHO by sex, the highest prevalence was found in the RIDF criteria for women with 5.92% (5.43—6.41), and the ATP III criteria for men with 2.29% (1.95–2.62). Comparatively, the lowest prevalence was found among women using the IDF criteria with 4.34% (3.96—4.73), and men using the JIS criteria with 1.63% (1.35—1.92). The prevalence of MHO in women was more than twice that of men, regardless of the definition (Table 1).

Demographics and underlying condition

The mean age of people with MHO based on ATP III criteria was 46.93 years old. Regarding all definitions, individuals with MHO were younger than those with MUO (46.93 vs 51.29, respectively, $p < 0.001$). (Supplementary Table 2) According to AHA-NHLBI, the age group of 35–44 had the highest prevalence of MHO in all definitions with 8.33% (7.2—9.45), whereas the age group above 75 had the lowest MHO prevalence in all definitions with 3.7% (1.79—5.61). A similar pattern was almost seen among age groups based on sex (Table 2). Across all definitions, MHO prevalence has decreased with age. The prevalence of MUO, however, has increased with age (Fig. 1).

We compared demographics, metabolic profiles, and health behaviors among MHO and MUO populations. (Supplementary Table 2) The WC and hip circumference (HC) of MHO cases and the mean systole and diastole of their blood pressure were lower than those of MUO cases on all definitions we studied. ($p < 0.001$). Blood glucose, HbA1C, total cholesterol, triglycerides, and ALT among those with MHO were lower than those among people with MUO. ($p < 0.001$) We found no significant relationship between MHO and alcohol consumption. ($p = 0.348$) Our study found that MUO prevalence was higher in all subcategories of alcohol consumption, smoking, education level, area of residence, positive family history of diabetes, occupation, marital status, presence of microalbuminuria, and wealth index, so we could not find any relationship between MHO

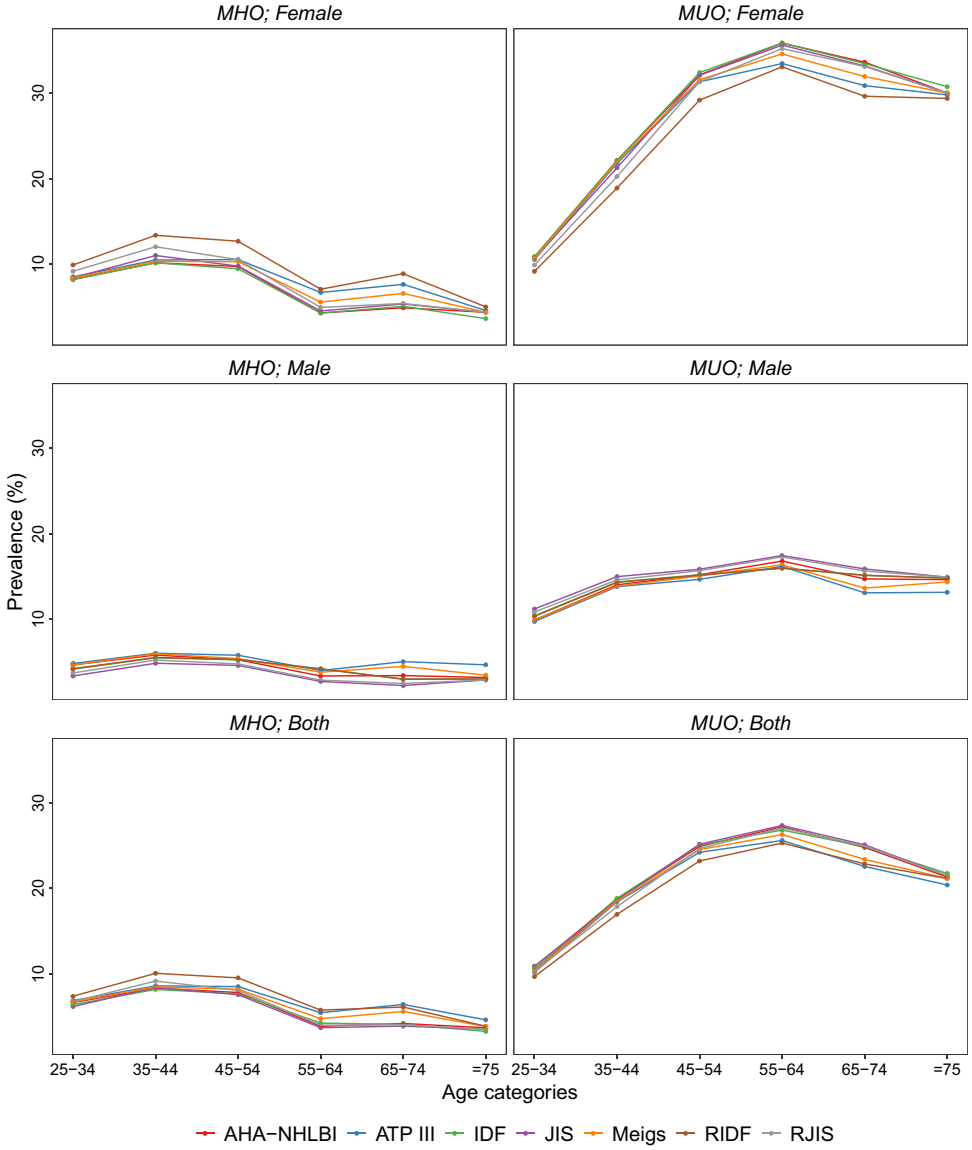

Fig. 1 Prevalence of MHO and MUO across age groups and sexes using different criteria

and MUO in these categories. (subgroups of these variables may be found in Supplementary Table 2).

Logistic regression analysis for the prediction of CVD

By all definitions, MUO individuals had more odds ratio significantly to being in the high-risk group by Framingham criteria than MHOs. For instance, according to the AHA-NHLBI criteria, the risk of having high-risk Framingham (CVD risk > = 20%) was more than seven times higher in MUO than in MHO. (Table 3) Ultimately, according to binary logistic regression analysis, all metabolically unhealthy groups had higher adjusted odds of cardiovascular disease.

As shown in Table 3, we assessed the association between metabolic status and CVD risk by stratifying the value by types of criteria. Regardless of all definitions, MUO individuals had a significantly more odds ratio of being in the high-risk group by Framingham criteria than MHOs. For instance, in Table 3, according to the AHA-NHLBI criteria, the risk of having high-risk Framingham in MUO was approximately seven times more than that of MHO. Table 3 provides the ORs and 95% CIs of high-risk Framingham according to metabolic health and obesity phenotypes. After adjusting (Table 3), among all definitions, the OR values for high-risk Framingham for the MUO ranged between 2.15 (95% CI: 0.98–4.68) andd 5.74 (3.08,10.67), as compared with MHO. The analysis of adjusted OR also revealed that the risk of having high-risk Framingham was increased for people with metabolically unhealthy (MU) with BMI < 25 and MU with 25 < = BMI < 30 in all definitions, as compared with metabolically healthy people at the same BMI. Ultimately, according to binary logistic regression analysis, all metabolically unhealthy groups had higher adjusted odds of cardiovascular disease.

Table 3 Crude and adjusted Odds Ratios of being high-risk according to Framingham score (CVD risk > =20%) in relation to metabolic health status

Variable	CRUDES			Adjusted[1]			CRUDES			Adjusted			CRUDES			Adjusted		
	MH[2], BMI < 25	MU[3], BMI < 25	*P* value	MH, BMI < 25	MU, BMI < 25	*P* value	MH, 25 < =BMI < 30	MU, 25 < =BMI < 30	*P* value	MH, 25 < =BMI < 30	MU, 25 < =BMI < 30	*P* value	MH, 30 < =BMI	MU, 30 < =BMI	*P* value	MH, 30 < =BMI	MU, 30 < =BMI	*P* value
Framingham AHA_NHLBI[4]	1	3.551 (2.636,4.783)	< 0.001	1	2.206 (1.46,3.334)	< 0.001	1	5.809 (4.385,7.697)	< 0.001	1	3.155 (2.209,4.505)	< 0.001	1	7.101 (3.806,13.249)	< 0.001	1	4.233 (2.187,8.195)	< 0.001
N (%) of high risk	251 (52.07%)	231 (47.93%)	482	251 (52.07%)	231 (47.93%)	482	100 (16.31%)	513 (83.69%)	613	100 (16.31%)	513 (83.69%)	613	16 (4.16%)	369 (95.84%)	385	16 (4.16%)	369 (95.84%)	385
Framingham ATPIII[5]	1	3.577 (2.645,4.838)	< 0.001	1	2.556 (1.697,3.85)	< 0.001	1	5.702 (4.363,7.452)	< 0.001	1	3.904 (2.779,5.486)	< 0.001	1	7.545 (4.192,13.581)	< 0.001	1	5.742 (3.088,10.678)	< 0.001
N (%) of high risk	266 (55.19%)	216 (44.81%)	482	266 (55.19%)	216 (44.81%)	482	116 (18.92%)	497 (81.08%)	613	116 (18.92%)	497 (81.08%)	613	19 (4.94%)	366 (95.06%)	385	19 (4.94%)	366 (95.06%)	385
Framingham JIS[6]	1	4.78 (3.605,6.337)	< 0.001	1	3.139 (2.198,4.483)	< 0.001	1	8.245 (5.827,11.666)	< 0.001	1	3.784 (2.524,5.671)	< 0.001	1	9.493 (4.495,20.049)	< 0.001	1	5.64 (2.586,12.3)	< 0.001
N (%) of high risk	202 (41.91%)	280 (58.09%)	482	202 (41.91%)	280 (58.09%)	482	56 (9.14%)	557 (90.86%)	613	56 (9.14%)	557 (90.86%)	613	12 (3.12%)	373 (96.88%)	385	12 (3.12%)	373 (96.88%)	385
Framingham RJIS[7]	1	4.534 (3.364,6.11)	< 0.001	1	2.938 (1.945,4.44)	< 0.001	1	7.719 (5.656,10.536)	< 0.001	1	3.595 (2.489,5.193)	< 0.001	1	10.058 (4.876,20.749)	< 0.001	1	5.668 (2.657,12.088)	< 0.001
N (%) of high risk	239 (49.59%)	243 (50.41%)	482	239 (49.59%)	243 (50.41%)	482	72 (11.75%)	541 (88.25%)	613	72 (11.75%)	541 (88.25%)	613	13 (3.38%)	372 (96.62%)	385	13 (3.38%)	372 (96.62%)	385
Framingham IDF[8]	1	2.044 (1.439,2.905)	< 0.001	1	1.509 (0.982,2.319)	0.061	1	3.213 (2.339,4.413)	< 0.001	1	1.606 (1.097,2.351)	0.015	1	3.604 (1.724,7.534)	0.001	1	2.151 (0.988,4.685)	0.054
N (%) of high risk	342 (70.95%)	140 (29.05%)	482	342 (70.95%)	140 (29.05%)	482	114 (18.60%)	499 (81.40%)	613	114 (18.60%)	499 (81.40%)	613	20 (5.19%)	365 (94.81%)	385	20 (5.19%)	365 (94.81%)	385
Framingham RIDF[9]	1	3.333 (2.17,5.118)	< 0.001	1	2.101 (1.29,3.422)	0.003	1	4.575 (3.456,6.056)	< 0.001	1	2.354 (1.693,3.274)	< 0.001	1	3.733 (2.025,6.883)	< 0.001	1	2.532 (1.323,4.844)	0.005
N (%) of high risk	394 (81.74%)	88 (18.26%)	482	394 (81.74%)	88 (18.26%)	482	158 (25.77%)	455 (74.23%)	613	158 (25.77%)	455 (74.23%)	613	29 (7.53%)	356 (92.47%)	385	29 (7.53%)	356 (92.47%)	385

Table 3 (continued)

Variable	CRUDES			Adjusted[1]			CRUDES			Adjusted			CRUDES			Adjusted		
	MH[2], BMI < 25	MU[3], BMI < 25	*P* value	MH, BMI < 25	MU, BMI < 25	*P* value	MH, 25 < = BMI < 30	MU, 25 < = BMI < 30	*P* value	MH, 25 < = BMI < 30	MU, 25 < = BMI < 30	*P* value	MH, 30 < = BMI	MU, 30 < = BMI	*P* value	MH, 30 < = BMI	MU, 30 < = BMI	*P* value
Framing-ham	1	3.631 (2.688,4.904)	< 0.001	1	2.538 (1.685,3.82)	< 0.001	1	5.894 (4.479,7.755)	< 0.001	1	3.75 (2.643,5.319)	< 0.001	1	7.034 (3.907,12.664)	< 0.001	1	4.757 (2.556,8.852)	< 0.001
Meigs																		
N (%) of high risk	261 (54.15%)	221 (45.85%)	482	261 (54.15%)	221 (45.85%)	482	107 (17.46%)	506 (82.54%)	613	107 (17.46%)	506 (82.54%)	613	19 (4.94%)	366 (95.06%)	385	19 (4.94%)	366 (95.06%)	385

[1]Age, physical activity, area, school years, wealth index, and current cigarette smoking were adjusted variables in the model

[2]Metabolically healthy

[3]Metabolically unhealthy

[4]American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI)

[5]Adult Treatment Panel III (ATP III)

[6]Joint Interim Statement (JIS)

[7]Regional JIS (RJIS)

[8]International Diabetes Federation (IDF)

[9]Regional IDF

Discussion

Our findings revealed that approximately one quarter of obese individuals met the criteria for MHO across all seven definitions used in both sexes. We observed a significantly higher prevalence of MHO among females than among males, irrespective of the definition used. Additionally, the prevalence of MHO decreased with advancing age. We also found regional disparities in MHO prevalence, although these differences were not statistically significant across the various definitions. Factors associated with MHO included younger age, lower waist circumference (WC), hip circumference (HC), blood sugar levels, HbA1c, cholesterol, triglycerides, ALT, eGFR, and higher HDL levels.

In terms of prevalence, the BioSHaRE study [8] reported an obesity prevalence of 17% and an MHO prevalence of 12% among adults in Europe in 2014. Wen et al. [33] analyzed data from eight National Health and Nutrition Examination Surveys (NHANES) in the US and found an increasing trend in MHO prevalence from 5.0% in 1999–2000 to 8.9% in 2013–2014. In our survey, the prevalence of obesity in Iran was 27.1%, with MHO prevalence ranging from 6.22% to 7.93% across the different criteria. In Europe, the MHO prevalence ranged from 1.1 to 6.6% and in Korea, MHO prevalence ranged from 5.7% to 25.8%, with the ATPIII criteria being the most commonly used for defining metabolic abnormalities [34].

Regarding regional differences within Iran, Latifi et al. [35] reported a 19.5% MHO prevalence in Ahvaz, Khuzestan province, using the ATP III criteria, while our study showed a prevalence of 8.51% in the same province. Similarly, Hajian-Tilaki et al. [36] found a 15.1% MHO prevalence in Babol, Mazandaran province, using ATP III criteria, whereas our study reported a prevalence of 7.98% (4.78–11.18) in Mazandaran province. These variations in prevalence can be attributed to differences in population characteristics, regional lifestyle habits, and the components of MHO definitions [37].

Consistent with previous studies [8, 33, 38], we observed a higher prevalence of MHO among women compared to men. In our survey, the prevalence of MHO among women was more than twice as high as that among men. This gender disparity can be attributed to differences in glycemic indices, body fat distribution, adipocyte size and function, hormonal regulation of body weight and adiposity, and the effects of estrogen on the accumulation of risk factors associated with metabolic syndrome [8].

It also demonstrated that transition from MHO to MUO was observed in approximately 50% of individuals initially classified as MHO, while 10% achieved a metabolically healthy normal weight after weight reduction [39]. According to Mathis et al., the transition between MHO and MUO involves a number of factors, such as excessive reactive oxygen species, oxidized oils, hormonal changes such as high

adiponectin as a chief insulin sensitizer in MHO, increased leptin and ghrelin in MUO, lower levels of inflammatory cytokines in MHO, deficiencies in nutrients, genetics and social factors as well as environmental pollution and age [40]. Vascular dysfunction resulting from obesity may contribute to metabolic disturbances [41]. Age also plays a role in the transition, and our findings support the decreased likelihood of MHO with aging, aligning with previous studies [42]. The highest prevalence of MHO observed in the 35 to 44 age group in our study supports the hypothesis that MHO is associated with an earlier onset of obesity [33, 38].

The increasing prevalence of MUO with aging can be partly explained by the prevalence of obesity phenotypes as individuals age. Moreover, the decline in estrogen's protective effect on the metabolic state in women with aging may contribute to the transition from MHO to MUO [43–45].

Iranians, according to Mahi et al., who analyzed 2015 data from the United Nations Population Division, were ranked second among countries aging the fastest between 2015 and 2050 for the percentage point increase in elderly people over the age of 60. In 2050, 56.8% of the population will be older than 60 (about 52.5 million people), a figure four times higher than in 2015 [46]. Considering these statistics, we expect that as Iranians' ages increase in the future, their prevalence of MHO will decrease, but their population of MUO will increase, and we will see an increase in cardiovascular complications in the future, based on our results [46]. Consequently, it is crucial for Iranian policymakers to prepare strategies to address these future challenges.

The presence of obesity is an independent risk factor for CVD [47]. Consistent with a meta-analysis by Eckel et al. [13], our study demonstrated that MUO individuals faced higher cardiovascular risks compared with MHO participants. In contrast to our findings, Li et al. reported that MHO and MUO phenotypes had similar cardiovascular risks with poor prognoses. It was found that MHO population had worse microvascular functions than MHNW population, suggesting that obesity does not have a benign effect on vascular health [47].

There has been speculation that blood pressure as a metabolic criterion may be an indication of changes in the vasculature resulting from aging and ultimately a possible cause of CVD and death [48]. Moreover, our study, similar to other studies [49], revealed that WC was lower in MHO than in MUO, indicating that MHO is negatively related to waist circumference. WC demonstrated great specificity and sensitivity when identifying high cardiovascular risks estimated by Framingham [49]. It has been proven that aging and higher WC were significantly correlated with all metabolically unhealthy states [45]. MHO is significantly associated with a reduced risk of atrial fibrillation when compared with MUO in obese participants [50, 51].

By examining microvasculature with venous occlusion plethysmography, scientists concluded that vascular function had abnormal vascular reactivity and impairment in MHO individuals compared to those with normal weight, although they showed less endothelial dysfunction than MUO participants [47]. MHO participants have also been shown to have a significant risk of developing diabetes, indicating that healthy obese individuals need to monitor their blood glucose levels, blood pressure, and lipid levels closely to stay at the metabolically healthy stage. In order to reduce cardiometabolic disease, healthy lifestyle habits require to be increased among high-risk populations [52].

To sum up, complications in obesity are not necessarily related to obesity phenotype but may be linked to metabolic dysfunction and visceral fat distribution rather than obesity phenotype [36].

In the current study, the analysis of adjusted OR also revealed that the risk of having high-risk Framingham was increased for people with metabolically unhealthy (MU) with BMI < 25 and MU with 25 < = BMI < 30 in all definitions, as compared with metabolically healthy people at the same BMI. A previous study found that metabolic disturbances led to further impairment of microvascular function in people regardless of their BMI category [47].

Although, the current study showed that the metabolically healthy population has a lower risk of CVD, but, in a meta-analysis involving studies with more than 10 years of follow-up, metabolically healthy overweight and obese people were found to have a greater risk of death. Even without metabolic dysfunction, prolonged exposure to excess weight has been associated with a higher risk of cardiovascular disease [53]. For future studies, it could be evaluated the risk of CVD among obese individuals, particularly MHO and MUO subgroups, with known CVD predictor biomarkers such as B-type natriuretic peptide or cardiac troponin, or with novel ones like endocan, which has been shown to be an independent predictor of CVD [54, 55]. As, it has been shown that elevated endocan levels, as a novel inflammatory endothelial biomarker, are in individuals with obesity and cardiovascular diseases. It may be due to the correlation between endocan and metabolic syndrome criteria, including alterations in lipid profiles, WC, and glycemic status, such as diabetes [55, 56].

In this study, we found that those with MHO have a higher GFR than those who have MUO. Prior research indicated that there was a higher incidence of CKD in in individuals with MHO than in those without obesity; thus losing weight appears to be a protective factor against developing kidney failure in MHO individuals [39]. Similar to Velho et al.'s study [38], we were not able to find a direct correlation between alcohol consumption and smoking and MHO, most likely because the prevalence of unhealthy metabolism in every group of smokers and alcohol consumers is higher than that of MHO. In line with recent studies, we demonstrated that MHO population had favorable metabolic profiles, including no hypertension, favorable lipid, and liver enzymes levels [57].

Strengths and limitations

An important strength of this study is the large sample size and the weighted cluster sampling method that was used, which can be considered reflective of the Iranian population. Furthermore, to our knowledge, there has never been a national or subnational study of MHO in Iran, along with a study of different definitions, prior to this. Only two previous studies reporting prevalence rates of MHO in the northern provinces of Iran and Ahvaz city, based on ATP III criteria, have ever been conducted [35, 36].

Moreover, to our knowledge, few studies have compared the prevalence of MHO using seven different definitions. Another strengths of the current study in this regard is using Regional IDF and Regional JIS which Iran's National Committee on obesity recommended that ethnicity-specific values be applied to the IDF and JIS definitions of obesity which have separate cutoffs for WC called Regional IDF and Regional JIS, respectively. Given the cross-sectional nature of this study, further longitudinal research is necessary to examine the potential associations between MHO and factors such as smoking, alcohol consumption, and physical activity. Additionally, a structured questionnaire was used to collect data which might be with some over-reporting or underreporting. In spite of these limitations, our article provides a clear overview of the importance of MHO in Iranian society.

Conclusion

This study contributes to our understanding of MHO in the Iranian context and underscores the importance of addressing obesity and metabolic health as part of public health initiatives. The findings reveal that approximately one-quarter of the obese population in Iran falls under the category of MHO, with a higher prevalence observed among women compared to men. The prevalence of MHO decreases with advancing age, while MUO becomes more prevalent. While having MHO appears to be associated with a lower risk of CVD compared to MUO, it is important to bear in mind that MHO is not without its own health risks and may lead to an unhealthy metabolic state. These findings emphasize the need for policymakers to implement strategies that prevent the transition from MHO to MUO and promote better health outcomes among individuals with MHO.

Furthermore, the study highlights the importance of using standardized definitions for MHO, as different criteria yielded similar prevalence rates. It is crucial for future research to employ consistent definitions to facilitate accurate comparisons across studies and populations.

Abbreviations *CI*: Confidence intervals; *CVD*: Cardiovascular disease; *MHO*: Metabolically healthy obesity; *MHNW*: Metabolically healthy normal weight; *FRC*: Framingham Risk Calculator; *ATP III*: Adult Treatment Panel III; *IDF*: International Diabetes Federation; *RIDF*: Regional IDF; *AHA-NHLBI*: American Heart Association/ National Heart, Lung, and Blood Institute; *JIS*: Joint Interim Statement; *RJIS*: Regional JIS

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Authors' contributions APL: Writing—original draft/ Conceptualization/ Formal analysis/ Visualization, YF: Formal Analysis/ Methodology/ Review & editing, MM: Formal Analysis/Methodology ZSV: Supervision/ Writing—original draft, MM, SSM, MKH, NA, EG, RH: Methodology/ Data curation, SS: Conceptualization/ Methodology APL, ZSV, SS, MMR, SR, MK, AK, AZ, MY, NF, MN, ADM, EA, SD, NGR, FF: Review & editing. FF, BL, NGR, NR: Investigation/ Resources/ Project administration. All authors read and approved the final manuscript.

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Data availability The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate The study methodology conformed to Helsinki Declaration standards as revised in 1989. The Ethical Committee approved the study of the National Institute for Health Research under reference number IR.TUMS.NIHR.REC.1398.006. All participants provided written informed consent prior to participation in the study. Moreover, the data used in the study did not include any identifiable personal information of participants, and the confidentiality of the data and the results are preserved.

Consent for publication Not applicable.

Competing interests The authors declare that they have no competing interests.

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