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META ANALYSIS

The long-term prognosis of heart diseases for different metabolic phenotypes: a systematic review and meta-analysis of prospective cohort studies

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Abstract

Purpose This meta-analysis aimed to assess the association of different categories of weight and metabolic status with risk of heart diseases including myocardial infarction (MI), cardiovascular diseases (CVDs), and heart failure (HF).

Methods Data from relevant studies were identified systematically by searching PubMed and Scopus search engines up to 29 May 2018. Prospective studies were included in the analyses with metabolically healthy normal weight (MHNW) as the reference. Pooled RRs and 95% CI were calculated using random-effects or fixed-effect models when appropriate. Subgroup analysis was applied to define possible sources of heterogeneity.

Results Overall, 21 studies ($n = 778{,}401$ participants) were eligible for the present meta-analysis. Generally, the risk of CVDs for all metabolic phenotypes in metabolically unhealthy obese increased compared with the MHNW group. A significant positive association between all metabolic phenotypes and the risk of HF was also observed expect for MHOW (RR = 1.10, 95% CI: 0.60–2.00, $P = 0.76$) and MHO phenotypes (RR = 0.96, 95% CI: 0.25–3.77, $P = 0.95$). Moreover, MUHO phenotype was associated with greater risk of MI compared with the MHNW phenotype (RR = 1.82, 95% CI: 1.50–2.22, $P < 0.001$, respectively).

Conclusions Our findings showed that all metabolically unhealthy phenotypes in different categories of weight were associated with increased incident of CVDs/HF and MI. Furthermore, healthy overweight and obese subjects had increased risk of CVDs.

Keywords BMI · Obesity · Metabolic healthy · Metabolic unhealthy · Cardiovascular diseases · Risk · Myocardial infarction · Heart failure

Abbreviations

ATPIII	Adult Treatment Panel III
BMI	body mass index
BP	blood pressure
BF	body fat
CVDs	cardiovascular diseases
CIs	confidence intervals
JCDGC	Joint Committee for Developing Chinese Guidelines
JIS	Joint Interim Statement
FBG	fasting blood glucose
HDL-C	high-density lipoprotein cholesterol
HRs	hazard ratios
HOMA-IR	homeostatic model assessment-insulin resistance
hs-CRP	high-sensitivity C-reactive protein
HF	heart failure
IMT	intima-media thickness

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IR	insulin resistance
LDL-C	low-density lipoprotein cholesterol
IDF	International Diabetes Federation
MI	myocardial infarction
MH	metabolically healthy
MHNW	metabolically healthy normal weight
MHO	metabolically healthy obese
MHOW	metabolically healthy overweight
MUH	metabolically unhealthy
MUHNW	metabolically unhealthy normal weight
MUHO	metabolically unhealthy obese
MUHOW	metabolically unhealthy overweight
MOOSE	meta-analysis of observational studies in epidemiology
MetS	metabolic syndrome
NW	normal weight
NOS	Newcastle-Ottawa scale
ORs	odds ratios
OB	obesity
OW	overweight
RRs	relative risks
T2D	type 2 diabetes
TG	triglyceride
TyG	triglyceride glucose
WC	waist circumference
WHO	World Health Organization

Introduction

Obesity is considered to be one of the most important risk factors for heart diseases [1, 2]. There are many adverse effects of obesity including disturbances in metabolic components: insulin resistance (IR), blood pressure (BP), and blood lipids [3–5], which are associated with heart diseases.

Recently, it is reported that a subgroup of obese (OB) individuals did not show metabolic abnormalities, despite their increased adiposity. This subgroup has been referred to as metabolically healthy OB (MHO) [6, 7]. The prevalence of MHO is 10–34% based on the criteria and populations used in studies. These individuals are characterized by preserved insulin sensitivity, normal BP, inflammation, and lipid profiles [8, 9]. Moreover, there exist normal-weight subjects who display abnormal metabolic profiles and increased risk of cardiovascular diseases (CVDs). Thus, a spectrum of metabolic healthy (MH) phenotypes according to body mass index (BMI) or body composition exists, ranging from metabolically healthy normal weight (MHNW) to metabolically unhealthy OB (MUHO). In short-term follow-ups, MHO was considered to be a benign condition [10] but, the development of clinical CVD events from the associated risk factors usually requires a long period of time [11]. Generally, there is no evidence that these individuals are permanently protected from the risk of obesity-related comorbidities [12]. Finding of studies investigating the effect of different obesity phenotypes on risk of CVDs are conflicting. Some studies have reported that MHO individuals are not at increased risk of developing CVDs compared to the MHNW group [13–16] while other studies report that MHO subjects are at increased risk of CVDs [11, 17, 18]. Findings of a meta-analysis involving 584,799 participants confirmed a positive association between the MHO phenotype and risk of CVDs, although, this study did not evaluate the association of CVDs with metabolically unhealthy normal weight (MUHNW)/MUHO/metabolically unhealthy overweight (MUHOW) phenotypes [19]. Another meta-analysis [20] of 14 cohort studies with a total of 299,059 participants also reported people with metabolically healthy overweight (MHOW)/MHO phenotypes and MUHNW were at increased risk for CVDs. However, they did not assess risk of heart failure (HF) and myocardial infarction (MI) in different metabolic phenotypes.

Finding of prospective studies reporting the risk heart disease events were associated with the different phenotypes metabolic with conflicting results. This systematic review and meta-analysis of cohort observational studies aimed to determine the effect of metabolic status (healthy and unhealthy) on risk of heart diseases (MI, CVDs, and HF) in normal weight (NW), overweight (OW), and OB subjects.

Methods

This meta-analysis was conducted according to the Meta-analysis of Observational Studies in Epidemiology guidelines[21].

Data sources and searches

We searched for all published observational studies that described the associations of heart diseases with different metabolic phenotypes and different categories of weight. A systematic literature search was performed using the electronic databases supplemented with the manual review of the reference list of obtained articles in PubMed and Scopus up to May 29, 2018, using the following relevant keywords: “Cardiovascular Diseases” OR “CVD” OR “ coronary artery disease OR “ coronary artery stenosis” OR “CAD” OR “ angina” OR “Stroke” OR “coronary artery blockage” OR “Atherosclerosis” OR “Ischemia” OR “myocardial infarction” OR” MI” OR “acute coronary syndrome” OR “st elevation myocardial infarction” OR “non-st elevation myocardial infarction” OR “heart failure” OR “heart failure,

congestive" OR "HF" AND "Obesity" OR "Body Mass Index" OR "BMI" OR "Overweight" OR "Adiposity" OR " Metabolically benign" OR "benign obesity" OR "healthy obesity" OR "metabolically healthy obesity" OR "metabolically benign obesity" OR "Metabolically healthy". The search was restricted to the published English articles. In the next step, literature searches were downloaded into EndNote (version ×6, for Windows, Thomson Reuters, Philadelphia, PA, USA) to merge retrieved citations, remove duplications, and to comfort the review process.

Study selection

Two independent authors (A.M. and S.S.-B.) reviewed the titles and abstracts of all the studies identified. Relevant articles of cohort were obtained and included in the present review if they: (1) were conducted in general population aged more than 18 years; (2) reported the incidence of heart diseases as the outcome including MI, CVDs, and HF; (3) reported criteria used for definition of metabolically healthy/unhealthy (MH/MUH) phenotypes; (4) reported risk estimates including relative risks (RRs), hazard ratios (HRs), or odds ratios (ORs), and the corresponding 95% confidence intervals (CIs) of heart diseases for each category; (5) reported the duration of follow-up; and (6) reported criteria used to definite the weight of subjects.

Studies were excluded if they were: literature reviews, cross sectional studies, republished data, case reports, cell and animal studies, gray literature, congress abstracts, dissertations, and patents, the information could not be extracted, were non-English studies, and did not report risk of heart diseases.

Data extraction and quality assessment

A.M. reviewed the full texts of the selected eligible studies and extracted the following information: first author's last name, year of publication, number of participants/cases in each category, mean age and/or age range of participants, sex, country, criterion used to define weight of participant, continent, duration of follow-up, criterion used to define MH/MUH phenotypes, sample size, diagnosis criteria for heart diseases, confounding factors that were adjusted for in the multivariable analysis, and reported HRs/RRs/ORs with their corresponding 95% CIs of heart diseases incidence for each category. Where further details were required, we contacted study authors for additional information. If there was disagreement, the third investigator resolved it. Newcastle–Ottawa Scale was used to assess quality of cohort studies. Studies with a score of 7 or higher were considered as high quality and those with a score of 3–7 as moderate quality.

Inigo et al. reported the risk of MI in relation to metabolic phenotypes was investigated based on different criteria. To conduct meta-analysis and avoid double-counting, we combined risk estimates to obtain a pooled effect size for each phenotypes [22].

Data synthesis and analysis

The category of MHNW group was used as the reference group to assess the risks of heart diseases. RRs and 95% CIs were considered the effect size in all studies. The reported ORs or HRs from studies was considered the equivalent of RRs. Pooled RRs with 95% CIs were calculated for heart diseases based on MUHNW, MHOW/MHO, and MUHOW/MUHO phenotypes. Heterogeneity among the studies was evaluated by the Cochran Q test and I^2 statistics. The heterogeneity was considered significant if either the Q statistic had $P < 0.1$ or $I^2 > 50\%$ [24]. When heterogeneity was significant, the random-effects model was conducted [25, 26]. To find possible sources of heterogeneity, we carried out subgroup analyses based on sex (female, male, and both) and continent, sample size, and duration of follow-up. Sensitivity analysis was also used to evaluate the unusually large influence of an individual study or a group of studies on the results. Publication bias was tested for by funnel plots, and Egger's and Begg's tests ($P < 0.10$). All statistical analyses for the current meta-analysis were performed with STATA version 14.0 (Stata Corporation, College Station, TX). P values < 0.05 were considered statistically as significant.

Results

Study screening

The flowchart of article selection is shown in Fig. 1. In all, 760 references were identified through electronic searches and 10 by manual searches, of which 300 were duplicates and 365 non-relevant, and thus excluded on the initial screening of titles and abstracts. Of the remaining, another 84 articles we excluded (detailed reasons for the exclusions are given in Fig. 1). Finally, 21 studies involving a total of 778,401 participants and 14,629 cases were included in our meta-analysis.

Study characteristics

The general demographic characteristics of the subjects in this meta-analysis are summarized in Table 1. Twenty-one studies reported the incident of heart diseases [3, 11, 13, 18, 22–38] that included 778,401 participants and 14,629 cases, however, because of the different types of heart diseases, we separately analyzed studies according to the incident of HF, MI, and CVDs. Two studies assessed incident of HF with

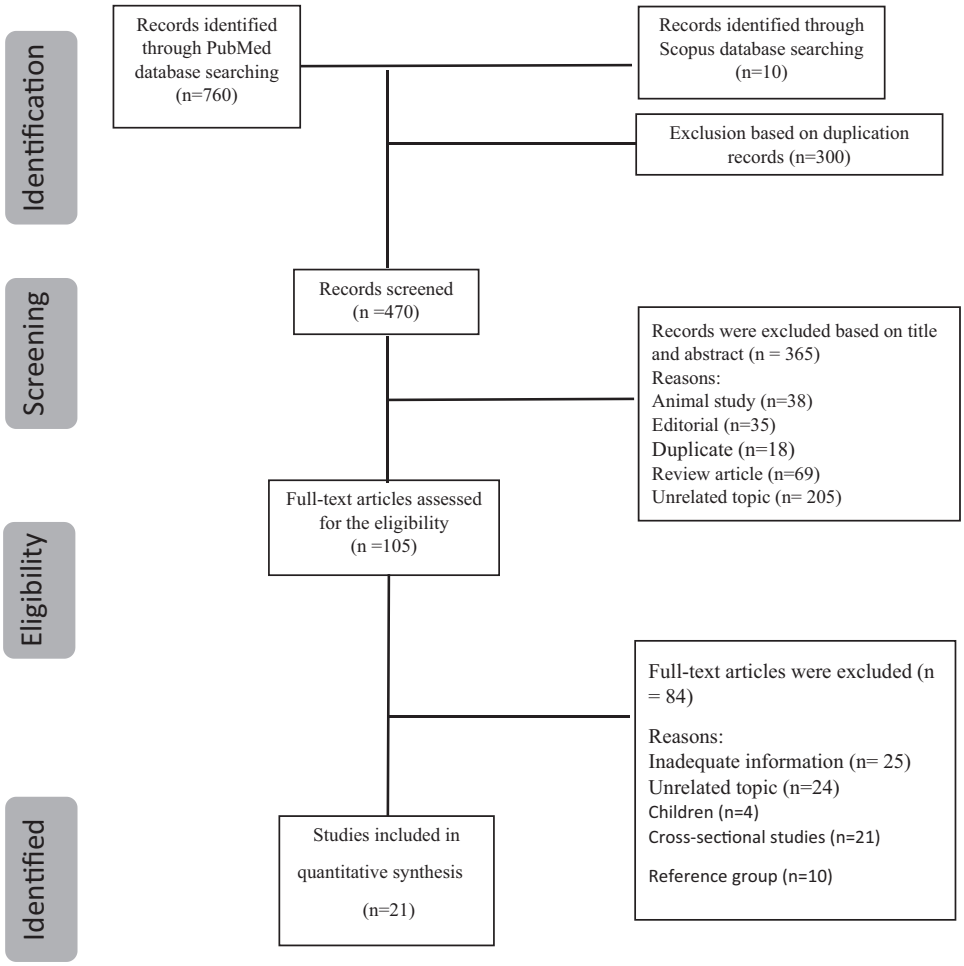

Fig. 1 PRISMA flowchart describing the study's systematic literature search and study selection

[37, 38] 61,849 individuals and 1386 cases, 5 studies reported incident of MI [22, 26, 28, 36, 38] with 166,009 subjects and 3854 cases and 18 assessed incident of CVDs [3, 11, 13, 18, 23–36] with 711,375 subjects and 9389 cases. These studies were published between 2004 and 2017. The age of subjects was over 18 years. Among the included studies, 7 were from the Asian populations [27, 29–31, 34–36], 5 were from American populations [18, 23–26], 8 were from European populations [3, 11, 22, 28, 32, 33, 37, 38], and 1 was from Australian populations [13]. According to World Health Organization criteria [41] subjects classified based on their BMI as NW (18.5–24.9 kg/m^2) or OW (25–29.9 kg/m^2) and OB (≥30.0 kg/m^2 [11, 13, 27, 30, 33] but other studies used other cutoffs for categories of BMI: in study of Luo et al. [36], body fat percentage (BF%) > 25% for men or BF% > 35% for women were defined as being OB. Keihani et al. [35] was defined obesity using national waist circumference (WC) cutoff points ≥ 102 cm for men and ≥88 cm for women. The duration of follow-up was from 3 to 30 years. The results in the most of the studies were adjusted for the potential confounders, including age, sex, physical inactivity, and smoking status. Furthermore, the reference category was a MHNW group in all studies. The definition of MH/MUH phenotypes was based on criteria by the Adult Treatment Panel III (ATPIII) [11, 18, 22, 23, 25, 29, 37], International Diabetes Federation (IDF) [13, 27, 30, 35, 38], joint committee for developing Chinese guidelines [36], components metabolic syndrome (MetS) [24, 32, 34], modified ATPIII [3, 26], harmonized metabolic syndrome [28], triglyceride glucose index [22], Joint Interim Statement [31, 33], and Homeostatic model assessment-insulin resistance [31]. Based on quality control, 8 studies received 10 score [11, 18, 22, 28, 30, 31, 35, 38] and all other studies received 8–9 score [3, 13, 23–27, 29, 32–34, 36, 37].

Results for metabolic phenotypes

MUHNW phenotype

There were 17 studies [3, 11, 13, 18, 23–33, 35, 36] concerning MUHNW phenotype and risk of CVDs with 16,349 participants and 798 cases. The association between MUHNW and the risk of CVDs based on random-effects

Table 1 Description of the studies included in the meta-analysis

Studies	Country	Ethnicity	Age range	Sample size and incident cases (total/*N* morbidity)	Metabolic health criteria	Definition of obesity	Duration of follow-up (years)	Estimate (95% CI)	Criteria to diagnose disease	Adjusted variables in analyses	Quality Score
Studies of CVDs											
Kip et al. [23]	USA	American	≥20Only in female	Total (780/108)MHNW (132/13) MUHNW (52/14)MHOW (120/5)MHO (77/4) MUHOW (149/28) MUHO (250/44)	ATPIII	NW < 24.9OW = 25–29.9OB ≥ 30	3	MHNW = 1.0 (ref.)MUHNW = 2.12 (0.81–5.59) MHOW = 0.76 (0.23–2.56) MUHOW = 1.88 (0.81–4.23) MHO = 0.74 (0.19–2.84) MUHO = 2.01 (0.93–4.84)	By assessment of angiographic	Age, race, prior MI, COPD, history of CHD, number of lesion ≥ 50, physical activity level	8
St-Pierre et al. [24]	Canada	American	55 Only in male	Total (1824/NR)MHNW (512/NR) MUHNW (44/NR)MHOW (429/NR) MUHOW (130/NR) MHO (54/NR) MUHO (62/NR)	TG, HDL, LDL, Apo B, insulin, BP, hs-CRP	BMINW < 25OW = 25–29.9OB ≥ 30	13	MHNW = 1.0 (ref.)MUHNW = 3.01 (0.81–5.59) MHOW = 1.01 (0.7–1.45) MUHOW = 1.98 (1.29–3.05) MHO = 1.53 (0.19–2.84) MUHO = 1.81 (1.02–3.19)	The diagnosis of a first ischemic heart disease event included angina on typical effort, coronary insufficiency, nonfatal MI, and coronary death. Coronary insufficiency was diagnosed using the nomenclature of the Framingham Heart Study for unstable angina presentation with electrocardiogram changes (changes in ST segment and T wave	Age, smoking, and medication use at baseline	8
Meigs et al. [25]	USA	American	5345% male 55% female	Total (2902/542)MHNW (981/47) MUHNW (75/16)MHOW (881/69)MHO (236/19) MUHOW (327/45) MUHO (402/346)	ATPIII	NW < 25OW = 25–29.9OB ≥ 30	11	MHNW = 1.0 (ref.)MUHNW = 3.31 (1.68–5.41) MHOW = 1.30 (0.89–1.90) MUHOW = 2.02 (1.33–3.06) MHO = 1.48 (0.87–2.55) MUHO = 2.28 (1.54–3.38)	By standard Framingham Heart Study criteria	Age, sex, LDL-C, smoking	8

Table 1 (continued)

Studies	Country	Ethnicity	Age range	Sample size and incident cases (total/*N* morbidity)	Metabolic health criteria	Definition of obesity	Duration of follow-up (years)	Estimate (95% CI)	Criteria to diagnose disease	Adjusted variables in analyses	Quality Score
Song et al. [26]	USA	American	≥45Only in female	Total (25,626/724)MHNW (12,943/278) MUHNW (583/46) MHOW (6730/163) MHO (2925/77)MUHOW (1104/78) MUHO (1341/82)	Modified ATPIII	NW < 25OW = 25–29.9OB ≥ 30	10	MHNW = 1.0 (ref.)MUHNW = 2.33 (1.66–3.28) MHOW = 1.08 (0.87–1.33) MUHOW = 2.5 (1.82–3.43) MHO = 1.05 (0.66–1.66) MUHO = 1.85 (1.13–3.02)	Diagnoses confirmed by a committee of cardiologists and one neurologist	Age, randomized treatment assignment (vitamin E and aspirin), smoking, exercise, alcohol intake, total calorie intake, multivitamin use, parental history of MI, postmenopausal hormone use	9
Arnlov et al. [3]	Sweden	European	50Only in male	Total (1758/681)MHNW (891/287) MUHNW (64/30)MHOW (582/250) MHO (30/14) MUHOW (125/62) MUHO (66/38)	Modified ATPIII	NW < 25OW = 25–30OB > 30	30	MHNW = 1.0 (ref.)MUHNW = 1.63 (1.11–2.37) MHOW = 1.52 (1.28–1.8) MUHOW = 1.74 (1.32–2.30) MHO = 1.95 (1.14–3.34) MUHO = 2.55 (1.82–3.58)	Use of ICD-8, ICD9, ICD-10	Age, smoking status, LDL	9
Hosseinpanah et al. [27]	Iran	Asian	≥3043% male57% female	Total (6215/446)MHNW (1555/64) MUHNW (223/30) MHOW (1447/51) MHO (408/13)MUHOW (1288/162) MUHO(1294/126)	IDF	NW = 18.5–24.9OW = 25–29.9OB ≥ 30	8	MHNW = 1.0 (ref.)MUHNW = 2.1 (1.36–3.26) MHOW = 1.1 (0.76–1.61) MUHOW = 2.35 (1.71–3.22) MHO = 1.07 (0.59–1.96) MUHO = 2.35 (1.71–3.22)	CVD was defined as any coronary heart disease events, stroke (a new neurological deficit that lasted 24 h), or CVD death	Age, gender, exercise (reference, heavy), smoking (reference, never smoker), family history of premature CAD (reference, no), and high total cholesterol (reference,<24 mg/dl)	9
Appleton et al. [13]	Australia	Oceania	≥1839% male61% female	Total (3743/167)MHNW (1172/25) MUHNW	IDF	NW = 18.5–24.9OW = 25–29.9OB ≥ 30	8	MHNW = 1.0 (ref.)MUHNW = 1.15 (0.5–2.62)	Self-report	Age, sex, household income, highest education, physical	8

Table 1 (continued)

Studies	Country	Ethnicity	Age range	Sample size and incident cases (total/*N* morbidity)	Metabolic health criteria	Definition of obesity	Duration of follow-up (years)	Estimate (95% CI)	Criteria to diagnose disease	Adjusted variables in analyses	Quality Score
				(155/10) MHOW (873/34)MHO (454/15) MUHOW (516/36) MUHO (573/47)				MHOW = 1.17 (0.68–2.02) MUHOW = 1.39 (0.7–2.42) MHO = 1.16 (0.58–2.29) MUHO = 2.23 (1.31–3.79)		activity, LDL cholesterol	
Aung et al. [18]	USA	American	≥2545% male55% female	Total (3700/127)MHNW (1267/16) MUHNW (186/12) MHOW (964/26)MHO (382/18) MUHOW (441/25) MUHO (478/30)	ATPIII	NW < 25OW = 25–29.9OB ≥ 30	7	MHNW = 1.0 (ref.)MUHNW = 2.9 (1.13–6.4) MHOW = 1.7 (0.9–3.21) MUHOW = 2.5 (1.3–4.9)MHO = 3.9 (1.9–7.8) MUHO = 3.9 (2–7.4)	Self-reported MI, stroke, or coronary revascularization procedure at follow-up or any mention of cardiovascular death on the death certificate (ICD9)	Age, sex, ethnic origin, smoking, ethnic origin, family history of diabetes, FBS	10
Hinnouho et al. [11]	UK	European	39–6369.7% male30.3% female	Total (7122/791)MHNW (3100/239) MUHNW (649/116) MHOW (1636/164) MUHOW (1080/206) MHO (279/37)MUHO (378/66)	ATPIII	BMINW = 18.5–24.9OW = 25–29.9OB ≥ 30		MHNW = 1.0 (ref.)MUHNW = 2.08 (1.66–2.6) MHOW = 1.24 (1.01–1.51) MUHOW = 2.33 (1.84–2.7) MHO = 1.95 (1.37–2.77) MUHO = 2.44 (1.85–3.21)	CVD events included fatal CHD [defined by the (ICD) 9 codes 410–414 or ICD-10 codes I20–25]	Sex, socioeconomic status, marital status, ethnicity, physical activity, smoking, alcohol, fruits, vegetable consumption, CVD medication	10
Thomsen and Nordestgaard [28]	Denmark	European	5539.9% male41.1% female	Total (71,527/1545)MHNW (28,431/248) MUHNW (3021/87) MHOW (17,406/391) MUHOW	Harmonized metabolic syndrome	BMINW < 25OW = 25–29.9OB ≥ 30	3.6	MHNW = 1.0 (ref.)MUHNW = 1.03 (0.82–1.3) MHOW = 1.08 (0.95–1.24) MUHOW = 1.3 (1.13–1.49)	Diagnosis of ischemic heart disease based on ICD-10, Eighth Revision, codes 410–414 and 410; International Classification of Diseases, Tenth Revision, codes I20–I25	Age, sex, smoking, plasma, LDL level, lipid-lowering medication use (statins for approximately 97% of participants receiving such	10

Table 1 (continued)

Studies	Country	Ethnicity	Age range	Sample size and incident cases (total/*N* morbidity)	Metabolic health criteria	Definition of obesity	Duration of follow-up (years)	Estimate (95% CI)	Criteria to diagnose disease	Adjusted variables in analyses	Quality Score
				(11,173/400) MHO (4416/129)MUHO (7080/290)				MHO = 1.45 (1.2–1.77) MUHO = 1.67 (1.44–1.93)	and I21–I22) was collected from 2003 until 2011 by reviewing all hospital admissions	medication), aspirin use, and physical inactivity	
Luo et al. [36]	China	Asian	30–9043% male57% female	Total (2380/212)MHNW (1346/83) MUHNW (100/34)MHO (645/37) MUHO (289/58)	JDCG	NW = BF% < 25% for male, BF% < 35% for femaleOB = BF % ≥ 25% for male, BF% ≥ 35% for female	3.5	MHNW = 1.0 (ref.)MUHNW = 1.58 (0.68–2.48) MHO = 1.03 (0.53–1.53) MUHO = 1.41 (0.77–2.05)	Hospital records and death certificates and use of (NINCDS) diagnostic criteria and MONICA	Age, total cholesterol, TG, family history of CVDs	9
Keihani et al. [35]	Iran	Asian	≥3042.7% male57.3% female	Total (7122/638)MHNW (1739/55) MUHNW (1629/137) MHO (881/61)MUHO (2873/385)	IDF	NW = WC < 102 cm for male, <88 cm for femaleOB = WC ≥ 102 cm for male, WC ≥ 88 cm for female	10	MHNW = 1.0 (ref.)MUHNW = 1.56 (1.07–2.27) MHO = 1.64 (1.09–2.47) MUHO = 1.86 (1.29–2.67)	Diagnosis based on electrocardiographic results, biomarkers, cardiac symptoms, or angiography	Age, sex, smoking, educational level, physical activity history of premature coronary artery disease in family, FBS, TG, HDL, SBP	10
Twig et al. [29]	Israel	Asian	≥25Only in male	Total (31,504/198)MHNW (8536/13) MUHNW (6792/33) MHOW (3946/12) MHO (599/6) MUHOW (8209/73) MUHO (3422/61)	ATPIII	NW < 25OW = 25–29.9OB ≥ 30	6	MHNW = 1.0 (ref.)MUHNW = 2.01 (1.03–3.93) MHOW = 1.42 (0.61–3.31) MUHOW = 2.65 (1.36–5.17) MHO = 4.74 (1.59–13.11) MUHO = 5.16 (2.26–11.79)	Based on diagnostic procedure treadmill exercise test, ST segment depression, symptoms of angina, coronary angiography	Age, family history of CAD, LDL, WBC count, smoking status, physical activity, MI	9
Dhana et al. [30]	China	Asian	6840% male60% female	Total (5314/861)MHNW (1444/203) MUHNW (306/63) MHOW (1334/205) MHO (260/	IDF	NW = 18.5–24.9OW = 25–29.9OB ≥ 30	14	MHNW = 1.0 (ref.)MUHNW = 1.35 (1.02–1.8) MHOW = 1.08 (0.89–1.32) MUHOW = 1.32 (1.09–1.6)	Fatal coronary heart disease events are coded by using the definitions applied within the Cardiovascular Health Study and Atherosclerosis Risk in the Communities Study	Age, gender, smoking, total cholesterol, treatment for hyperlipidemia, estimated GFR, alcohol, physical	10

Table 1 (continued)

Studies	Country	Ethnicity	Age range	Sample size and incident cases (total/*N* morbidity)	Metabolic health criteria	Definition of obesity	Duration of follow-up (years)	Estimate (95% CI)	Criteria to diagnose disease	Adjusted variables in analyses	Quality Score
				36)MUHOW (1182/219) MUHO (788/135)				MHO = 1.07 (0.75–1.53)		activity, and education	
Mirzaei et al. [31]	Iran	Asian	≥3044.8% male55.2% female	Total (7167/712)MHNW (1322/56) MUHNW (1005/116) MHOW (794/28)MUHOW (2667/310) MHO (159/7) MUHO (1895/195)	JIS, HOMA-IR	BMINW < 25OW = 25–29.9OB ≥ 30	8.1	MHNW = 1.0 (ref.)MHUNW = 1.69 (1.18–2.43) MHOW = 1.22 (0.73–2.04) MUHOW = 2.04 (1.47–2.82) MHO = 1.74 (0.68–4.44) MUHO = 2.36 (1.67–3.55)	CHD included cases of definite MI (diagnostic ECG results and biomarkers), probable myocardial infarction (positive ECG findings plus cardiac symptoms or signs plus missing biomarkers or positive ECG findings plus equivocal biomarkers), unstable angina pectoris (new cardiac symptoms or changing symptom patterns and positive ECG findings with normal biomarkers), proven CHD by angiography, and CHD death	Age, sex, smoking, education level, physical activity, family history of premature CAD and total cholesterol	10
Kim et al. [34]	Korea	Asian	≥48Only in male	Total (6453/1314)MHNW (2215/589) MHOW (2165/680) MHO (1669/634)	TG, HDL, BP, FBG	BMINW = 18.5–22.9OW = 23–24.9OB > 25	4.2	MHNW = 1.0 (ref.)MHOW = 1.13 (1–1.28) MHO = 1.28 (1.09–1.51)	Subclinical carotid atherosclerosis was assessed using carotid ultrasonography and was defined as the presence of an abnormally increased CIMT or carotid plaque	Age, year of screening exam, smoking status, alcohol intake, regular exercise, and glomerular filtration rate, FBS, SBP pressure, TG, HDL, WC	9
Hansen et al. [32]	Denmark	European	≥20	Total (6238/323)MHNW (1603/34) MUHNW (1097/54) MHOW (878/25)MUHOW	BP, TG, FBG, HDL	BMINW < 25OW = 25–29.9OB ≥ 30	10	MHNW = 1 (ref.)for female: MUHNW = 1.9 (1–3.8)MHOW = 1.9 (0.9–3.7) MUHOW = 2.8 (1.5–5.1)MHO	To define IHD the ICD-10 codes I20–I25 and ICD-8 codes 410–413 were used	Age and intervention group at baseline, smoking, physical activity, dietary habits, cohabitation, and ethnicity, taking into	9

Table 1 (continued)

Studies	Country	Ethnicity	Age range	Sample size and incident cases (total/*N* morbidity)	Metabolic health criteria	Definition of obesity	Duration of follow-up (years)	Estimate (95% CI)	Criteria to diagnose disease	Adjusted variables in analyses	Quality Score
				(1592/126) MHO (172/12)MUHO (896/72)				= 2.2 (0.9–5.6) MUHO = 2.6 (1.3–5)for male: MUHNW = 2.4 (1.2–4.6) MHOW = 1.4 (0.7–3.1) MUHOW = 3.3 (1.8–6)MHO = 3 (1.2–7.7) MUHO = 3.4 (1.8–6.7)		account change in exposure status at the 5-year follow-up examination	
Lassale et al. [33]	England	European	35–7070.5% female29.5% male	Total (520,000/NR) MHNW (4282/NR) MUHNW (368/NR) MHOW (2761/NR) MUHOW (1403/NR) MHO (751/NR)MUHO (909/NR)	JIS	BMINW = 18.5–24.9OW = 25–29.9OB ≥ 30	12.2	MHNW = 1.0 (ref.)MUHNW = 2.15 (1.79-2.57)MHOW = 1.26 (1.14–1.4) MUHOW = 2.33 (1.97–2.76) MHO = 1.28 (1.03–1.58)	Incident CHD cases were defined as first CHD events, whether nonfatal or fatal, consisting of ICD-10 codes I20–I25, which include myocardial infarction, other acute ischemic heart diseases, chronic ischemic heart disease, and angina pectoris	Age, smoking, systolic blood pressure, total cholesterol, HDL, history of diabetes	8
Studies of HF											
Voulgari et al. [5]	Greece	European	60.345% male55% female	Total (550/185)MHNW (109/17) MUHNW (68/43)MHOW (127/18)MHO (43/4) MUHOW (107/51) MUHO (96/52)	ATPIII	NW ≤ 24.9OW = 25–29.9OB ≥ 30	6	MHNW = 1.0 (ref.)MUHNW = 2.33 (1.25–4.36) MHOW = 1.12 (0.35–1.33) MUHOW = 2.66 (1.73–4.13) MHO = 0.41 (0.1–1.31) MUHO = 2.13 (1.29–3.17)	Identified by the physician on the basis of symptoms and signs objective evidence of structural or functional heart	Age, sex, impaired glucose tolerance, dyslipidemia, hypertension, current cigarette smoking, physical activity, left ventricular hypertrophy function on echo cardiology	9
Morkedal et al. [38]	Norway	European		Total (61,299/1201)MHNW	IDF	NW < 25OW = 25–29.9OB ≥ 30	12	MHNW = 1.0 (ref.)MUHNW	Diagnosed by practicing cardiologists according	Age, sex, smoking status, time since	9

Table 1 (continued)

Studies	Country	Ethnicity	Age range	Sample size and incident cases (total/*N* morbidity)	Metabolic health criteria	Definition of obesity	Duration of follow-up (years)	Estimate (95% CI)	Criteria to diagnose disease	Adjusted variables in analyses	Quality Score
			≥2046% male54% female	(23,798/274) MUHNW (1032/46) MHOW (18,446/262) MHO (3479/97)MUHOW (7964/268) MUHO (6580/254)				= 1.1 (0.07–1.7) MHOW = 1 (0.08–1.3) MUHOW = 1.4 (1.1–1.7)MHO = 1.7 (1.3–2.3) MUHO = 1.7 (1.4–2.2)	to the European Society of Cardiology/American College of Cardiology consensus guideline	last meal, level of education, marital status, alcohol consumption	
Studies of MI											
Song et al. [26]	USA	American	≥45Only in female	Total (25,626/256)MHNW (12,943/129) MUHNW (583/12) MHOW (6730/56) MHO (2925/22)MUHOW (1104/19) MUHO (1341/18)	Modified ATPIII	NW < 25OW = 25–29.9OB ≥ 30	10	MHNW = 1.0 (ref.)MUHNW = 1.21 (0.63–2.34) MHOW = 0.72 (0.46–1.4) MUHOW = 1.5 (0.83–2.71) MHO = 0.82 (0.35–1.91) MUHO = 1.05 (0.42–2.66)	Diagnoses confirmed by a committee of cardiologists and one neurologist	Age, randomized treatment assignment (vitamin E and aspirin), smoking, exercise, alcohol intake, total calorie intake, multivitamin use, parental history of MI, postmenopausal hormone use	9
Thomsen and Nordestgaard [28]	Denmark	European	5539.9% male41.1% female	Total (71,527/744)MHNW (28,431/248) MUHNW (3021/36) MHOW (17,406/135) MUHOW (11,173/164) MHO (4416/46)MUHO (7080/115)	Harmonized metabolic syndrome	BMINW < 25OW = 25–29.9OB ≥ 30		MHNW = 1.0 (ref.)MUHNW = 1.39 (0.96–2.02) MHOW = 1.26 (1–1.6) MUHOW = 1.7 (1.35–2.15) MHO = 1.88 (1.34–2.63) MUHO = 2.33 (1.81–3)	Diagnosis of MI based on ICD-10, Eighth Revision, codes 410–414 and 410; International Classification of Diseases, Tenth Revision, codes I20–I25 and I21–I22 was collected from 2003 until 2011 by reviewing all hospital admissions	Age, sex, smoking, plasma, low-density lipoprotein cholesterol level, lipid-lowering medication use (statins for approximately 97% of participants receiving such medication), aspirin use, and physical inactivity	10
Morkedal et al. [38]	Norway	European	≥2046% male54% female	Total (61,299/2547)MHNW (23,798/593) MUHNW	IDF	NW < 25OW = 25–29.9OB ≥ 30	12	MHNW = 1.0 (ref.)MUHNW = 1.9 (1.4–2.5) MHOW = 1.3	Diagnosed by practicing cardiologists according to the European Society of Cardiology/American	Age, sex, smoking status, time since last meal, level of education, marital	10

Table 1 (continued)

Studies	Country	Ethnicity	Age range	Sample size and incident cases (total/*N* morbidity)	Metabolic health criteria	Definition of obesity	Duration of follow-up (years)	Estimate (95% CI)	Criteria to diagnose disease	Adjusted variables in analyses	Quality Score
				(1032/88) MHOW (18,446/663) MHO (3479/111)MUHOW (7964/616) MUHO (6580/476)				(1.1–1.5) MUHOW = 1.7 (1.5–1.9)MHO = 1.1 (0.09–1.4) MUHO = 2 (1.7–2.3)	College of Cardiology consensus guideline	status, alcohol consumption	
Luo et al. [36]	China	Asian	30–9043% male57% female	Total (2380/138)MHNW (1346/45) MUHNW (100/32)MHO (654/27) MUHO (289/34)	JCDCG	NW = BF% < 25% for male, BF% < 35% for femaleOB = BF % ≥ 25% for male, BF% ≥ 35% for female	3.5	MHNW = 1.0 (ref.)MUHNW = 1.54 (0.41–2.66) MHO = 1.44 (0.54–2.34) MUHO = 0.9 (0.27–1.53)	Hospital records and death certificates and use of (NINCDS) diagnostic criteria and MONICA	Age, total cholesterol, TG, family history of cardiovascular disease	9
Sánchez-Inigo et al. [22]	Spain	European	55.656% female44% male	Total (5177/169)MHNW (3374/92) MUHNW (805/33)MHO (697/21) MUHO (481/23)	ATPIII TyG index	BMINW < 30OB ≥ 30	9.1	MHNW = 1 (ref.)MUHNW = 1.32 (1.22–1.43) [a]MUHO = 1.65 (1.47–1.84) [a]MHO = 1.03 (0.93–1.15)[a]	Stroke was diagnosed according to The International Classification of Diseases, Tenth Revision (ICD-10)	Age, sex, BMI, cigarette smoking, daily alcohol intake, lifestyle pattern, hypertension, coronary heart disease, type 2 diabetes, antiaggregation therapy, HDL LDL, and TG	10

ATPIII Adult Treatment Panel III, *IDF* International Diabetes Federation, *JCDCG* Joint Committee for Developing Chinese guidelines, *HOMA-IR* Homeostatic model assessment-insulin resistance, *MHNW* metabolically healthy normal weight, *MHO* metabolically healthy obese, *MHOW* metabolically healthy overweight, *MUHNW* metabolically unhealthy normal weight, *MUHO* metabolically unhealthy obese, *MUHOW* metabolically unhealthy overweight, *BMI* body mass index, *NW* normal weight, *OB* obesity, *OW* overweight, *WC* waist circumference, *LDL-C* low-density lipoprotein cholesterol, *hs-CRP* high-sensitivity C-reactive protein, *SBP* systolic blood pressure, *GFR* glomerular filtration rate, *WBC* white blood cell, *CVDs* cardiovascular diseases, *JIS* Joint Interim Statement, *TyG* triglyceride glucose, *SBP* systolic blood pressure, *IHD* ischemic heart disease, *TG* triglyceride, *HDL* high-density lipoprotein cholesterol, *BP* blood pressure, *ICD* International Classification of Disease, *CAD* coronary artery disease, *MI* myocardial Infarction, *COPD* chronic obstructive pulmonary disease, *CHD* coronary heart diseases, *ECG* electrocardiogram, *FBS* fasting blood glucose, *MONICA* monitoring of trends and determinants in cardiovascular disease, *NINCDS* National Institute of Neurological and Communicative Diseases and Stroke, *CIMT*: carotid intima-media thickness, *CI* confidence interval, *HF* heart failure, *MI* myocardial infarction, *NA* not available, *ref.* reference

[a]The calculated pooled effect size for MHO/MUHO, and MUHNW phenotypes

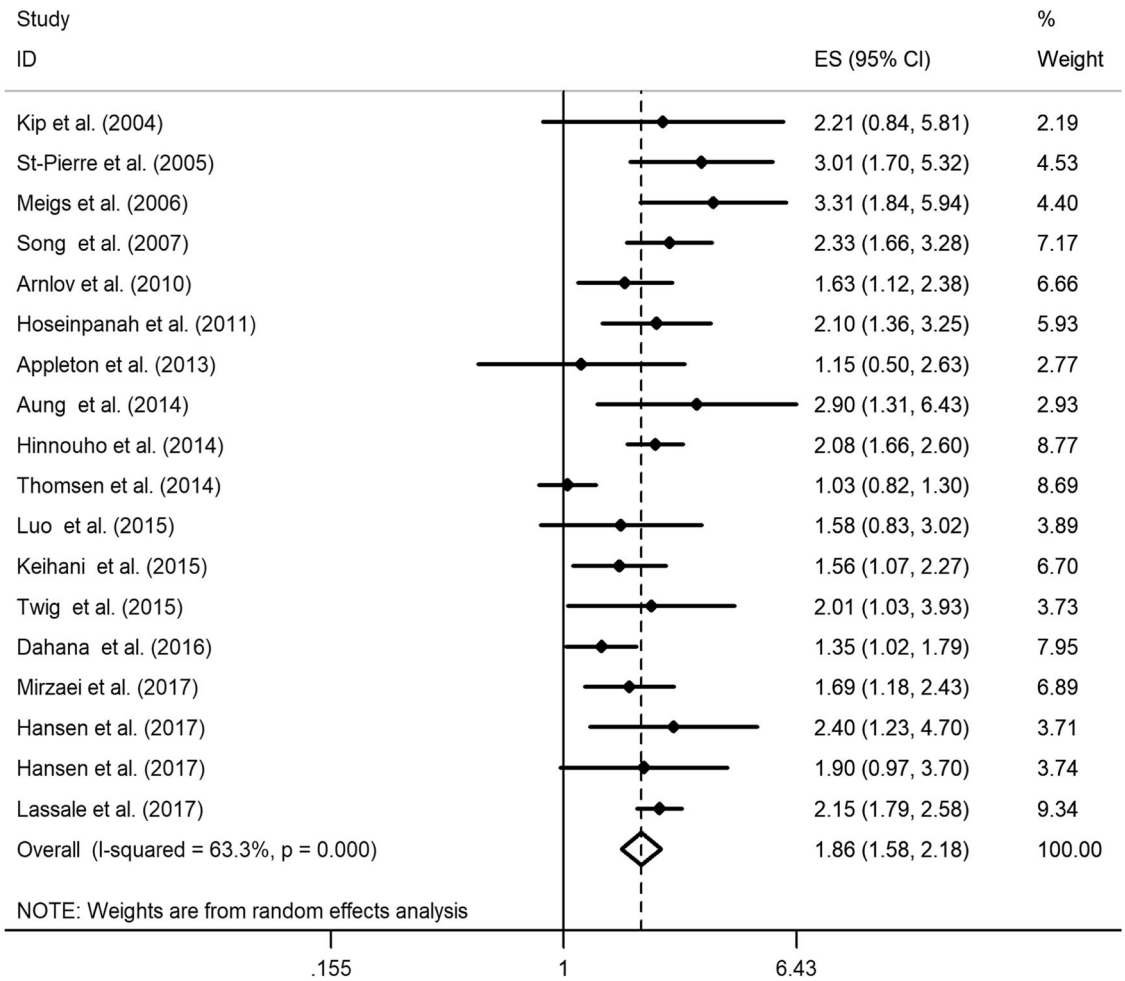

Fig. 2 Forest plot for the association between metabolically unhealthy normal weight phenotypes and the risk of cardiovascular diseases using a random-effects model

model (Fig. 2) was provided. There was a strong positive link between MUHNM and the risk of CVDs (pooled effect size: 1.86, 95% CI: 1.58–2.18, $P < 0.001$, $I^2 = 63.3\%$, $P_{\text{heterogeneity}} < 0.001$). Subgroup analysis showed that gender, sample size, and continent were as potential sources of between studies heterogeneity (Table 2). The association between MUHNW and the risk of CVDs was significant in all subgroups, except in one study, which conducted in Australia.

There were five studies [22, 26, 28, 36, 38] with 5541 subjects and 201 cases, regarding MUHNW phenotype and risk of MI. The association between all metabolic phenotypes and the risk of MI based on random-effects (Fig. 3) models was investigated. There were a strong positive association between MUHNW (pooled effect size: 1.44, 95% CI: 1.22–1.70, $P < 0.001$, $I^2 = 31.6\%$, $P_{\text{heterogeneity}} = 0.21$), with the risk of MI.

There were two studies [37, 38] with a total of 89 cases and 1100 participants in MUHNW phenotype and risk of HF. The association between all metabolic phenotypes and the risk of HF based on random-effects (Fig. 4) model was investigated. There was also a strong positive association between MUHNW (pooled effect size: 2.11, 95% CI: 1.18–3.77, $P = 0.01$, $I^2 = 0\%$, $P_{\text{heterogeneity}} = 0.39$) with the risk of HF.

MUHOW phenotype

There were 15 studies [3, 13, 18, 23–33, 39] that concerning MUHOW phenotype and risk of CVDs with 31,386 subjects and 1770 cases. The association between MUHOW and the risk of CVDs based on random-effects model (Fig. 5) was shown. There was a significant positive association between MUHOW and CVD (pooled effect size: 2.04, 95% CI: 1.73–2.41, $P < 0.001$, $I^2 = 76.3\%$, $P_{\text{heterogeneity}} < 0.001$). Gender, follow-up duration, sample size, and continent were found as sources of between studies heterogeneity (Table 2).

Table 2 Subgroup analysis based on fixed-effects models for the association between metabolic phenotypes and risk of CVDs and MI

Phenotypes	Subgroup	Number of effect sizes	RRs (95% CI)	P_{value}	I^2 (%)	$P_{within\ heterogeneity}$	$P_{between\ heterogeneity}$
CVDs							
MUHNW							
		18	1.79 (1.65–1.95)	<0.001	63.3	<0.001	
Gender							0.15
	Female	3	2.23 (1.67–2.98)	<0.001	0	0.86	
	Male	4	2.03 (1.56–2.65)	<0.001	10.6	0.34	
	Both	11	1.72 (1.57–1.89)	<0.001	74.3	<0.001	
Follow-up							<0.001
	<5	3	1.12 (0.91–1.38)	0.29	42.8	0.17	
	5–10	4	2.01 (1.48–2.73)	<0.001	0	0.45	
	≥10	11	1.96 (1.78–2.16)	<0.001	42.8	0.06	
Sample size							0.29
	<5000	9	2.08 (1.69–2.55)	<0.001	13.2	0.32	
	5000–10,000	5	1.75 (1.53–2.01)	<0.001	38.9	0.16	
	>10,000	4	1.72 (1.52–1.96)	<0.001	89.3	<0.001	
Continent							0.005
	America	5	2.63 (2.07–3.35)	<0.001	0	0.83	
	Europe	6	1.75 (1.57–1.96)	<0.001	82.5	<0.001	
	Asia	6	1.60 (1.36–1.89)	<0.001	0	0.63	
	Australia	1	1.15 (0.50–2.63)	0.74	0	0	
MUHOW							
		16	1.83 (1.70–1.96)	<0.001	76.3	<0.001	
Gender							<0.001
	Female	3	2.48 (1.90–3.24)	<0.001	0	0.74	
	Male	4	2.01 (1.64–2.48)	<0.001	30.3	0.23	
	Both	9	1.76 (1.63–1.90)	<0.001	84.5	<0.001	
Follow-up							<0.001
	<5	2	1.31 (1.15–1.50)	<0.001	0	0.38	
	5–10	4	2.39 (1.84–3.09)	<0.001	0	0.91	
	≥10	10	2.02 (1.85–2.20)	<0.001	70.3	<0.001	
Sample size							0.24
	<5000	8	2.05 (1.72–2.43)	<0.001	0	0.61	
	5000–10,000	4	1.86 (1.66–2.09)	<0.001	85	<0.001	
	>10,000	8	1.73 (1.57–1.92)	<0.001	91.5	<0.001	
Continent							0.14
	America	5	2.22 (1.82–2.72)	<0.001	0	0.86	
	Europe	6	1.82 (1.67–1.99)	<0.001	88.4	<0.001	
	Asia	4	1.67 (1.45–1.92)	<0.001	77.8	0.004	
	Australia	1	1.39 (0.25–7.69)	0.70	0	0	
MUHO							
		18	2.07 (1.92–2.22)	<0.001	66.3	0.0001	
Gender							0.12
	Female	3	2.07 (1.45–2.96)	<0.001	0	0.72	
	Male	4	2.66 (2.06–3.42)	<0.001	37.8	0.18	
	Both	11	2.02 (1.87–2.18)	<0.001	75.5	<0.001	
Follow-up							<0.001
	<5	3	1.66 (1.44–1.90)	<0.001	0	0.70	

Table 2 (continued)

Phenotypes	Subgroup	Number of effect sizes	RRs (95% CI)	P_{value}	I^2 (%)	$P_{within\ heterogeneity}$	$P_{between\ heterogeneity}$
	5–10	4	2.66 (2.09–3.38)	<0.001	37.5	0.18	
	≥10	11	2.19 (2.00–2.39)	<0.001	65.9	0.001	
Sample size							0.15
	<5000	9	2.31 (1.95–2.74)	<0.001	10.8	0.34	
	5000–10,000	5	1.88 (1.65–2.14)	<0.001	75.5	0.003	
	>10,000	4	2.10 (1.90–2.31)	<0.001	86	<0.001	
Continent							0.09
	America	5	2.22 (1.75–2.81)	<0.001	0	0.41	
	Europe	6	2.18 (1.99–2.38)	<0.001	76	0.001	
	Asia	6	1.77 (1.54–2.03)	<0.001	73.9	0.002	
	Australia	1	2.23 (1.31–3.79)	<0.001	0	0	
MI							
MUHO							
		5	1.80 (1.66–1.96)	<0.001	66.5	0.01	
Gender							0.24
	Female	1	1.05 (0.42–2.64)	0.91	0	0	
	Male	0	0	0	0	0	
	Both	4	1.81 (1.66–1.97)	<0.001	71.7	0.01	
Follow-up							0.05
	<5	2	2.16 (1.70–2.76)	<0.001	76.5	0.03	
	5–10	1	1.65 (1.47–1.85)	<0.001	0	0	
	≥ 10	2	1.97 (1.69–2.28)	<0.001	45.2	0.17	
Sample size							0.01
	<5000	1	0.90 (0.38–2.14)	0.81	0	0	
	5000–10,000	1	1.65 (1.47–1.85)	<0.001	0	0	
	>10,000	3	2.05 (1.81–2.34)	<0.001	35.6	0.21	
Continent							0.14
	America	1	1.05 (0.42–2.64)	0.91	0	0	
	Europe	3	1.82 (1.67–1.98)	<0.001	85.3	0.01	
	Asia	1	0.90 (0.38–2.14)	0.81	0	0	
	Australia	0	0	0	0	0	
MHOW							
		3	1.25 (1.10–1.42)	0.001	50.3	0.13	
Gender							0.04
	Female	1	0.72 (0.41–1.26)	0.24	0	0	
	Male	0	0	0	0	0	
	Both	2	1.29 (1.13–1.47)	<0.001	0	0.82	
Follow-up							0.93
	<5	1	1.26 (0.99–1.60)	0.05	0	0	
	5-10	0	0	0	0	0	
	≥10	2	1.25 (1.07–1.45)	0.004	75.1	0.04	
Sample size							0
	<5000	0	0	0	0	0	
	5000–10,000	0	0	0	0	0	
	>10,000	3	1.25 (1.10–1.42)	0.001	50.3	0.13	
Continent							0.04
	America	1	0.72 (0.41–1.26)	0.24	0	0	

Table 2 (continued)

Phenotypes	Subgroup	Number of effect sizes	RRs (95% CI)	P_{value}	I^2 (%)	$P_{within\ heterogeneity}$	$P_{between\ heterogeneity}$
	Europe	2	1.29 (1.13–1.47)	<0.001	0	0.82	
	Asia	0	0	0	0	0	
	Australia	0	0	0	0	0	
MHO							
		5	1.09 (0.99–1.20)	0.09	67	0.01	
Gender							0.50
	Female	1	0.82 (0.35–1.92)	0.64	0	0	
	Male	0	0	0	0	0	
	Both	4	1.09 (0.99–1.21)	0.08	74.3	0.009	
Follow-up							0.003
	<5	2	1.79 (1.32–2.44)	<0.001	0	0.56	
	5–10	1	1.03 (0.93–1.15)	0.58	0	0	
	≥10	2	0.89 (0.43–1.83)	0.75	0	0.72	
Sample size							0.01
	<5000	1	1.44 (0.69–3.00)	0.33	0	0	
	5000–10,000	1	1.03 (0.93–1.15)	0.58	0	0	
	>10,000	3	1.64 (1.22–2.23)	0.001	43.2	0.17	
Continent							0.61
	America	1	0.82 (0.35–1.92)	0.64	0	0	
	Europe	3	1.09 (0.98–1.20)	0.10	82	0.004	
	Asia	1	1.44 (0.69–3.00)	0.32	0	0	
	Australia	0	0	0	0	0	

MUHO metabolically unhealthy obese, *MUHNW* metabolically unhealthy normal weight, *MUHO* metabolically unhealthy obese, *MHO* metabolically healthy obese, *MI* myocardial infarction, *HF* heart failure, *CVDs* cardiovascular diseases

There were three studies [26, 28, 38] with 20,241 participants and 799 cases that have addressed the association of MUHOW phenotype and risk of MI. There were a strong positive association between MUHOW (pooled effect size: 1.69, 95% CI: 1.53–1.88, $P = 0.0001$, $I^2 = 0\%$, $P_{heterogeneity} = 0.92$) with the risk of stroke.

There were only two studies [37, 38] on the association of MUHOW phenotype and risk of HF with 8071 participants and 319 cases. Significant positive association was observed between MUHOW and HF (pooled effect size: 1.88, 95% CI: 1.00–3.51, $P = 0.04$, $I^2 = 85\%$, $P_{heterogeneity} = 0.01$).

MUHO phenotype

Seventeen studies [3, 11, 13, 18, 23–33, 35, 36] related with risk of CVDs that including of 1975 cases and 22,996 participants in MUHO phenotype. The association between MUHO and the risk of CVDs based on random-effects model (Fig. 6) was examined. Significant association was observed between MUHO and the increased risk of CVDs (pooled effect size: 2.16, 95% CI: 1.87–2.50, $P < 0.001$) with significant heterogeneity ($I^2 = 66.3\%$, $P_{heterogeneity} < 0.001$). Gender, follow-up duration, sample size, and continent were found as sources of between studies heterogeneity (Table 2).

There were five studies [22, 26, 28, 36, 38] with 15,771 participants and 666 cases, regarding risk of MI in MUHO phenotype. Significant positive relationship was found between MUHO and increased risk of MI (pooled effect size: 1.82, 95% CI: 1.50–2.22, $P < 0.001$, $I^2 = 66.5\%$, $P_{heterogeneity} = 0.01$).

There were two studies [37, 38] for risk of HF that regarding MUHOW phenotype with 6676 participants and 306 cases. MUHO was significantly associated with increased risk of HF (pooled effect size: 1.78, 95% CI: 1.45–2.18, $P < 0.001$) ($I^2 = 0\%$, $P_{heterogeneity} = 0.38$).

MHOW phenotype

There were 16 studies [3, 11, 13, 18, 23–34], regarding the association of MHOW phenotype and risk of CVDs with 42,946 subjects and 2103 cases. The association between MUHO and the risk of CVDs based on random-effects model has been shown in Fig. 7. A significant positive association was observed between MHOW and the risk of CVDs (pooled effect size: 1.20, 95% CI: 1.12–1.27, $P < 0.001$, $I^2 = 14\%$, $P_{heterogeneity} = 0.28$).

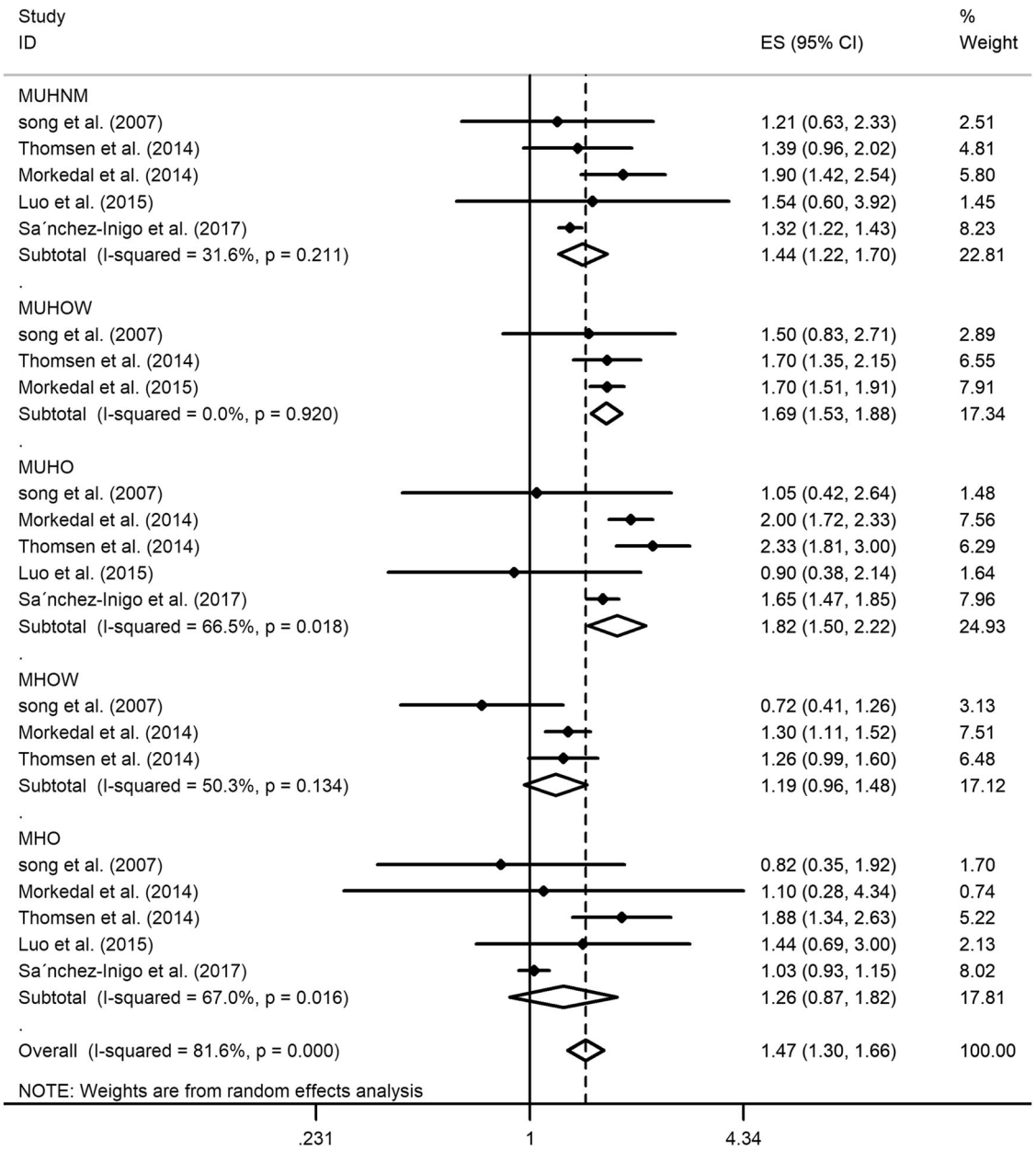

Fig. 3 Forest plot for the association between metabolic phenotypes and the risk of myocardial infarction using a random-effects model

There were three studies [26, 28, 38] that regarding the association of MHOW phenotype and risk of MI with 42,582 participants and 854 cases. There was no association between MHOW phenotype and risk of MI (pooled effect size: 1.19, 95% CI: 0.96–1.48, $P = 0.10$, $I^2 = 50.3\%$, $P_{\text{heterogeneity}} = 0.13$).

There were two studies [37, 38] for risk of HF with 18,573 cases and 280 participants that addressed the association of MHOW phenotype. MHOW did not show any relation regarding HF (pooled effect size: 1.10, 95% CI: 0.60–2.00, $P = 0.76$, $I^2 = 0\%$, $P_{\text{heterogeneity}} = 0.88$).

MHO phenotype

There were 18 studies [3, 11, 13, 18, 23–36] with 1119 cases and 14,397 participants in MHO group that reported risk of CVDs. The association between MHO and the risk of CVDs based on random-effects model has been shown in Fig. 8. There was a strong link between MHO phenotype and the increased risk of CVDs (pooled effect size: 1.46, 95% CI: 1.27–1.67, $P < 0.001$, $I^2 = 42.6\%$, $P_{\text{heterogeneity}} = 0.02$).

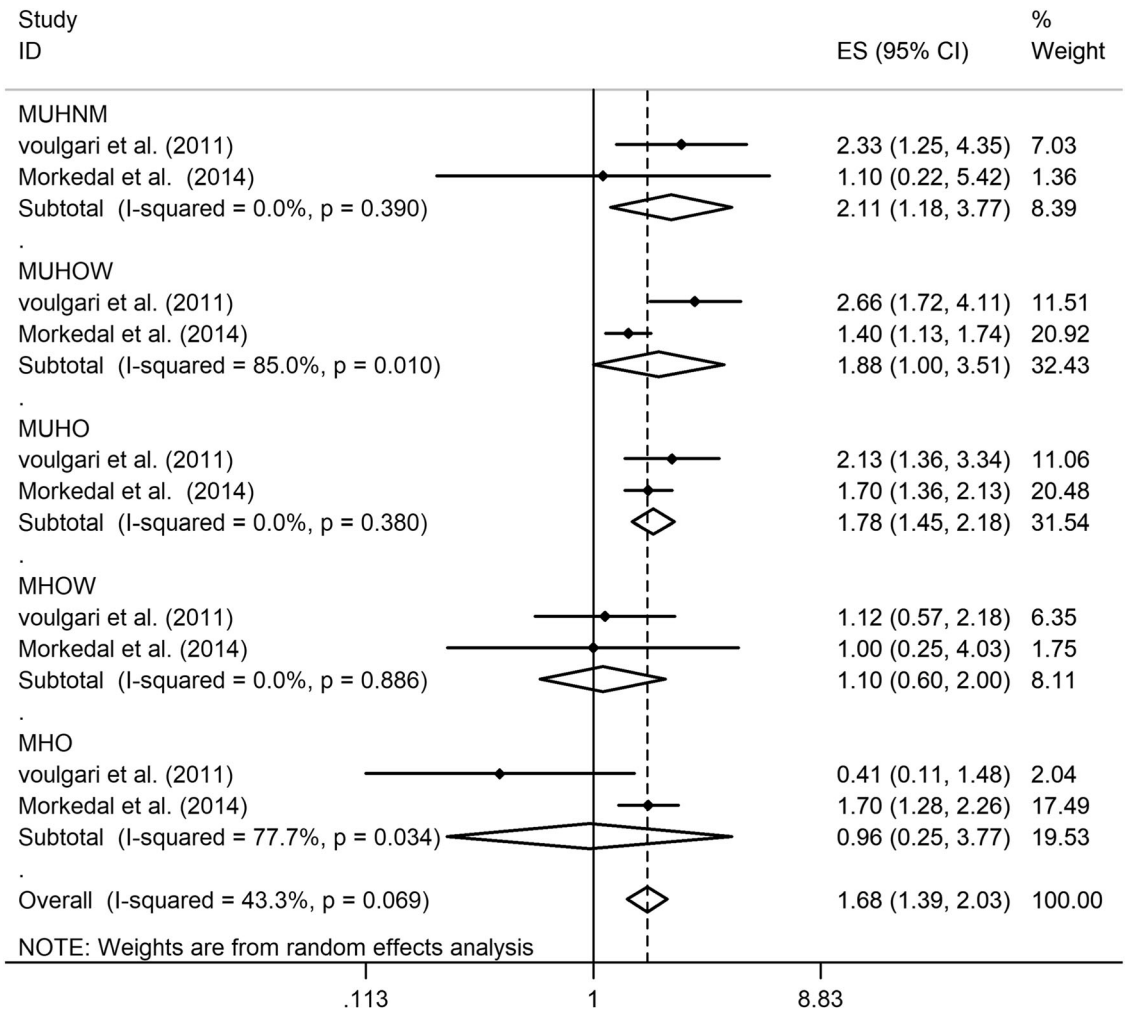

Fig. 4 Forest plot for the association between metabolic phenotypes and the risk of heart failure using a random-effects model

Five studies [22, 26, 28, 36, 38] addressed the association of MHO phenotype and risk of MI with 12,171 participants and 227 cases. No association was observed between MHO and the risk of MI in random-effects model (pooled effect size: 1.26, 95% CI: 0.87–1.82, $P = 0.22$, $I^2 = 67\%$, $P_{\text{heterogeneity}} = 0.01$).

There were only two studies [37, 38] that related with risk of HF in MHO phenotype with 3522 participants and 101 cases. MHO was not associated with increased risk of HF (pooled effect size: 0.96, 95% CI: 0.25–3.77, $P = 0.95$, $I^2 = 77\%$, $P_{\text{heterogeneity}} = 0.03$).

Sensitivity analysis

Findings demonstrated that the link between all kinds of metabolic phenotype and the risk of CVDs (Supplemental Fig. 1) and MI (Supplemental Fig. 2) did not depend on a single or couple of studies.

Publication bias

Visual inspection of funnel plot together with results of Egger test were applied to consider publication bias among studies. No evidence of publication bias was observed regarding the association of MUHNW ($P = 0.42$), MUHOW ($P = 0.10$), and MUHO ($P = 0.30$), MHOW ($P = 0.67$), and MHO ($P = 0.11$) with the risk of CVDs (Supplemental Fig. 3). In addition, we did not detect any publication bias regarding the association between MUHNW ($P = 0.44$), MUHOW ($P = 0.33$), and MUHO ($P = 0.73$), MHOW ($P = 0.19$), and MHO ($P = 0.50$) with the risk of MI (Supplemental Fig. 4).

Discussion

Our results showed that there was a positive association between MUH phenotypes and risk of heart diseases

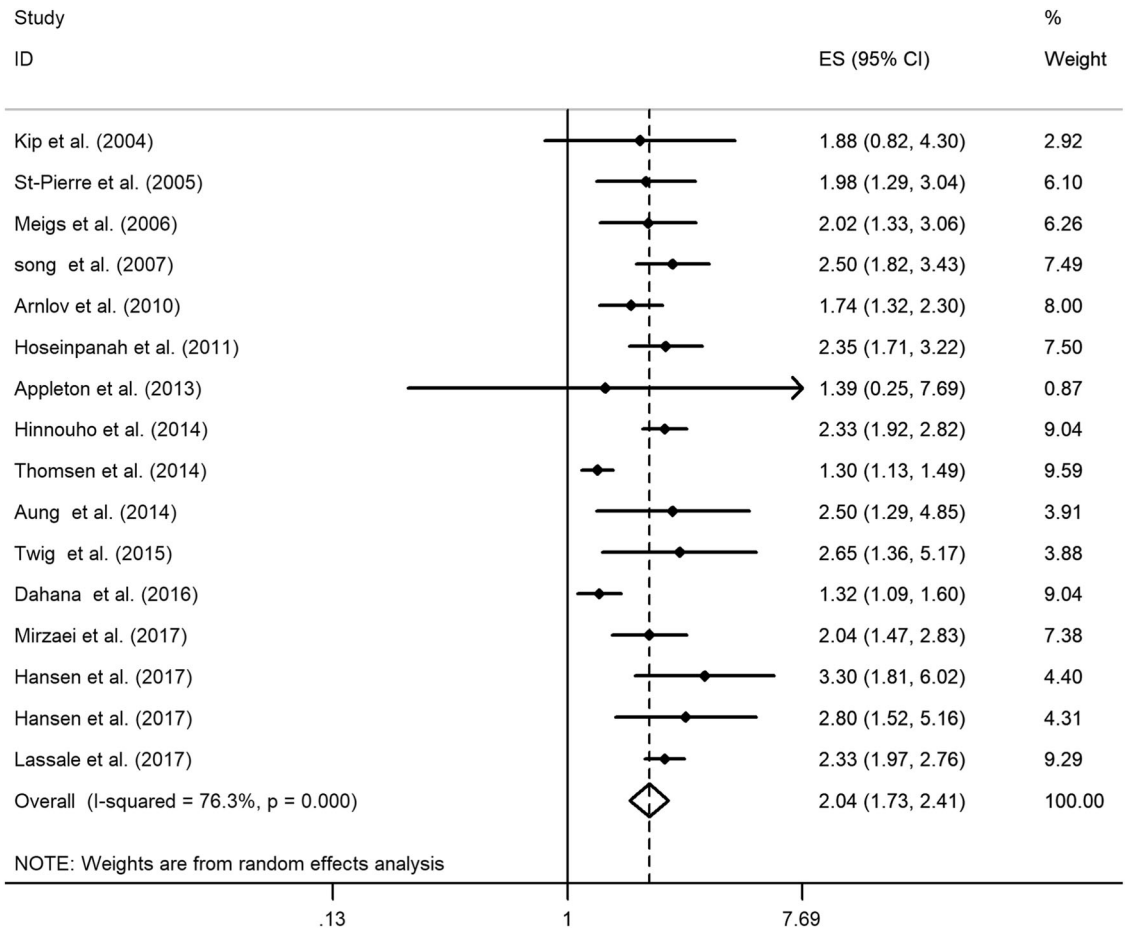

Fig. 5 Forest plot for the association between metabolically unhealthy overweight phenotypes and the risk of cardiovascular diseases using a random-effects model

(CVDs, HF, and MI) compared with MHNW phenotype. Overweight/OB individuals had significantly higher risk of CVDs regardless of the presence of MetS components while MHO/MHOW phenotypes were not associated with an increased risk of MI and HF.

Our finding showed that MUHO phenotype increased risk of CVDs. In agreement with recently published studies indicated that obesity and OW led into increased risk of CVDs in adults [2, 40, 41]. However, the pathophysiologic mechanism of this association is uncertain. This possibility is biologically acceptable because obesity is associated with IR, which appears to be the underlying cause of the MetS, hypertension and type 2 diabetes and to be an important link between components of the metabolic abnormalities [42, 43], which all are critical in promoting atherogenesis and fat deposits in the vessels. The present findings also indicate that normal-weight subjects with the MetS have a significantly increased CVDs risk. Meigs et al. [25], in an 11-year follow-up study of 2902 men and women, reported increased risk for CVDs events in normal-weight subjects with MetS compared to OB subjects without MetS (RR = 3.01 vs 1.48). In our study the risk for CVDs events in MUHNW phenotype was higher than MHO group was 86% (RR = 1.86 vs 1.40). Our finding also showed that MHO and MHOW phenotypes increased risk of CVDs compared to the MHNW group. One study showed that the MHO group had a significantly greater prevalence of coronary atherosclerosis compared with MHNW counterparts [44]. Khan et al. [45] found that MHO subjects had a significantly greater subclinical CVD burden, like common carotid artery intima-media thickness, and aortic and coronary calcification, compared with NW individuals.

In contrast to our results, Kip et al. [23] indicated that OW and OB women with normal metabolism have a relatively lower risk of CVDs (OR = 0.76, 95% CI = 0.23–2.56; OR = 0.74, 95% CI = 0.19-2.84, respectively) and suggested that the clinical evaluation of abnormal metabolism (ie, MetS and diabetes) should play a important role rather than the diagnosis of obesity per se in cardiovascular risk stratification in women.

Our results are in agreement with recently published studies. Aung et al. [18] reported that incidence of CVDs

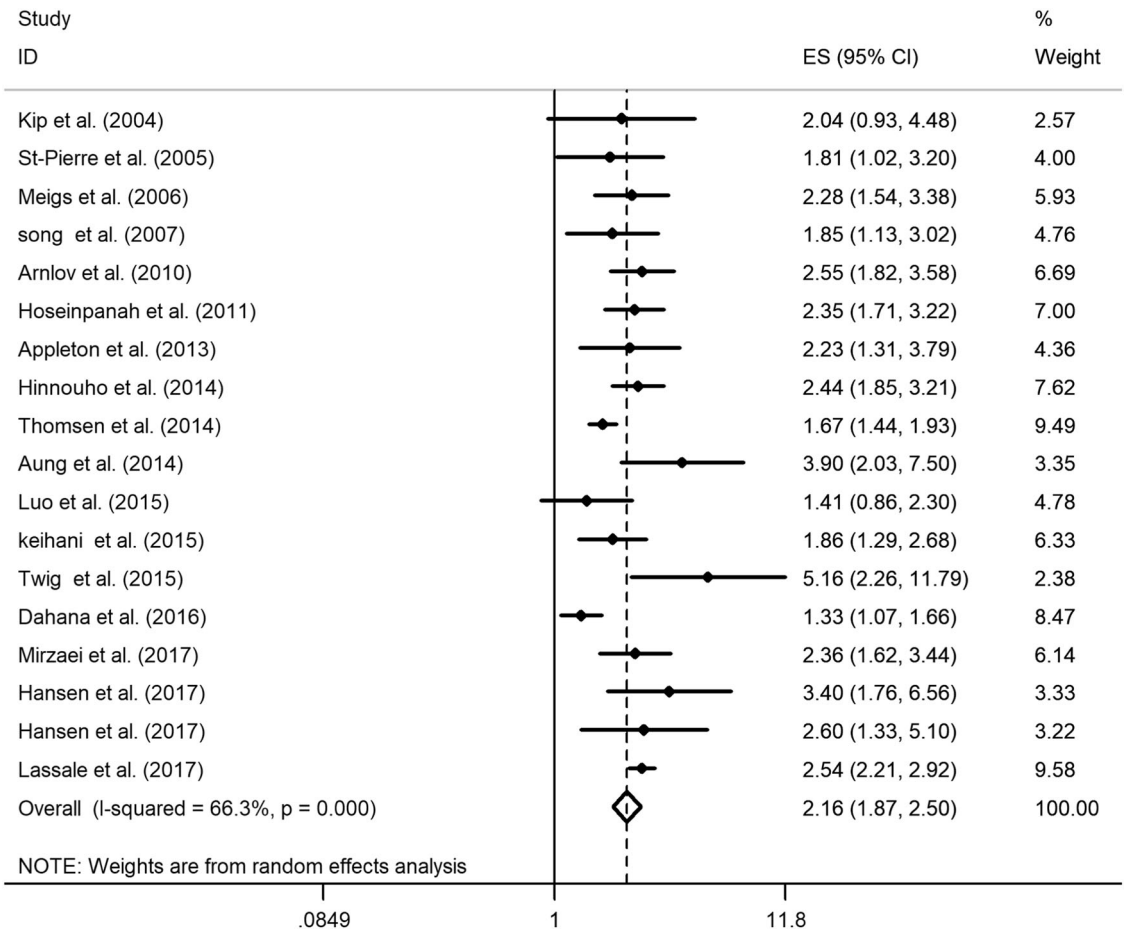

Fig. 6 Forest plot for the association between metabolically unhealthy obese phenotypes and the risk of cardiovascular diseases using a random-effects model

was increased in MHO individuals (RR = 3.9, 95% CI = 1.9–7.8). We believe that gender, sample size, continent, and follow-up duration differences may be responsible for the conflicting results among studies. Results were consistent across gender and continent categories except in one study that conducted in Australia with no association with an increased risk of CVDs in MUHNW/MUHOW phenotypes.

The present findings also indicate that MUH phenotypes in different categories of weight have a significantly increased risk of MI while in MHOW/MHO phenotypes the risk of MI increased, which was not statistically significant. One study reported that [28] risk of MI in MHOW and MHO individuals increased compared to NW subjects without MetS (OR = 1.26, 95% CI = 1–1.61, OR = 1.88, 95% CI = 1.34–2.63, respectively). In contrast, Sanchez-Inigo et al. [22] reported that in subjects with MHO the greater risk of MI was not observed while MU participants, OB and non-OB, had an increased risk of MI, which was in line with our findings.

The other finding was a significant association between MUHNW, MUHOW, and MUHO phenotypes with increased risk of HF. Although one study reported the effect of MetS on risk of incident of HF in a cohort of older adults failed to demonstrate a significant relationship between MetS and risk of incident HF [46], while a study by Ingelsson et al. [47] determined MetS as a significant and independent predictor of HF incidence in a population of middle-aged men without a baseline CVD history. There are numerous potential pathophysiologic mechanisms underlying the relationship between IR and HF. The heart may become less energy efficient in the setting of IR, with decreased glucose use and increased free fatty acid use. This metabolic deregulation may increase susceptibility to injury, such as pressure overload or ischemia and thus promote deleterious renin-angiotensin-aldosterone system activation [48].

Our results showed no significant association between MHOW/MHO phenotypes with increased risk of HF and MI. Overall, OW and obesity are risk factors for MI and HF; on the other hand, there is a time lag with regard to the

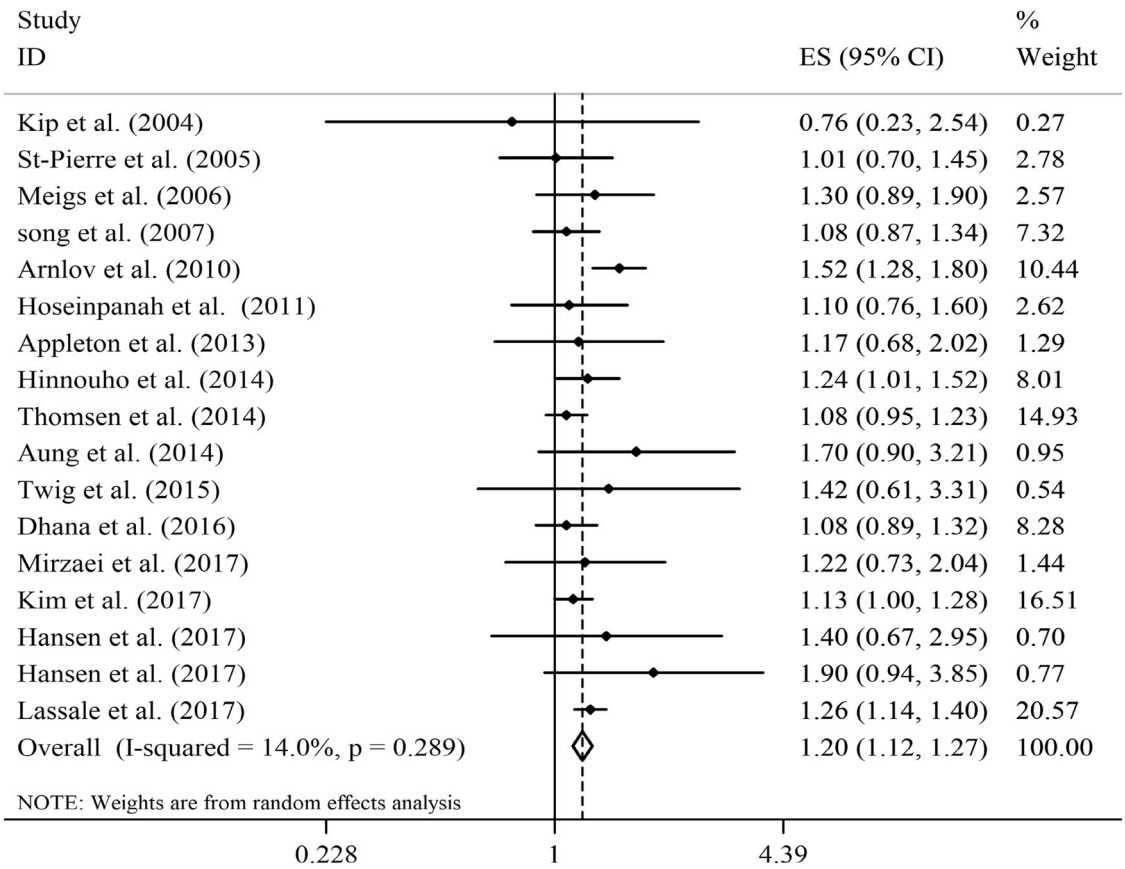

Fig. 7 Forest plot for the association between metabolically healthy overweight phenotypes and the risk of cardiovascular diseases using a random-effects model

long-term effect of MHO phenotype on risk of MI. Recent data have shown that MHO phenotype had intermediate burden of subclinical atherosclerosis between MHNW and MUHO groups, suggesting that these persons might be at increased risk but likely develop overt disease more slowly than their at-risk individuals [45].

This is the first meta-analysis to assess the risk of heart diseases including CVDs, MI and HF separately among metabolic phenotypes of different weight categories. The main strength of the current study is its large pooled sample size ($n = 778{,}401$) among adults, and this study has been conducted on large-scale prospective studies, which enabled the natural observation without intervention among stratified subgroups. Data for the pooled analysis were derived from fully adjusted models in the primary studies, which should reduce the likelihood of confounding.

However, there are some limitations in our study that should be noted. First, in some subgroups only a limited number of studies were identified, which made it difficult to draw a firm conclusion. Second, significant heterogeneity was observed in the analysis of MHOW/MHO and MUHNW/MUHOW/MUHO individuals. In addition, the studies also differed in definitions for MH/MUH status and criteria used for definition of obesity, which may partly result in between-study heterogeneity. Finally, however visual inspection of a funnel plot and the Egger's test for publication bias did not show that bias considerably affected our overall results; we recognize that this bias might still exist despite best efforts to perform a comprehensive search.

Conclusion

In the present meta-analysis, we summarized the combined effects of different categories of weight with the presence/absence of Mets on the risk of heart diseases (CVDs, HF, and MI). MUHO/MUHOW/MUHNW phenotypes had significantly increased incident of CVDs/MI and HF. MHOW/MHO individuals showed a remarkably higher risk for CVDs, while MHO/MHOW phenotypes was no associated with an increased risk of MI and HF. Screening for obesity and other metabolic abnormalities should be routinely performed in clinical practice to institute appropriate preventive measures. Additionally, we reaffirmed that a MH profile did not completely protect OB individuals from heart disease events.

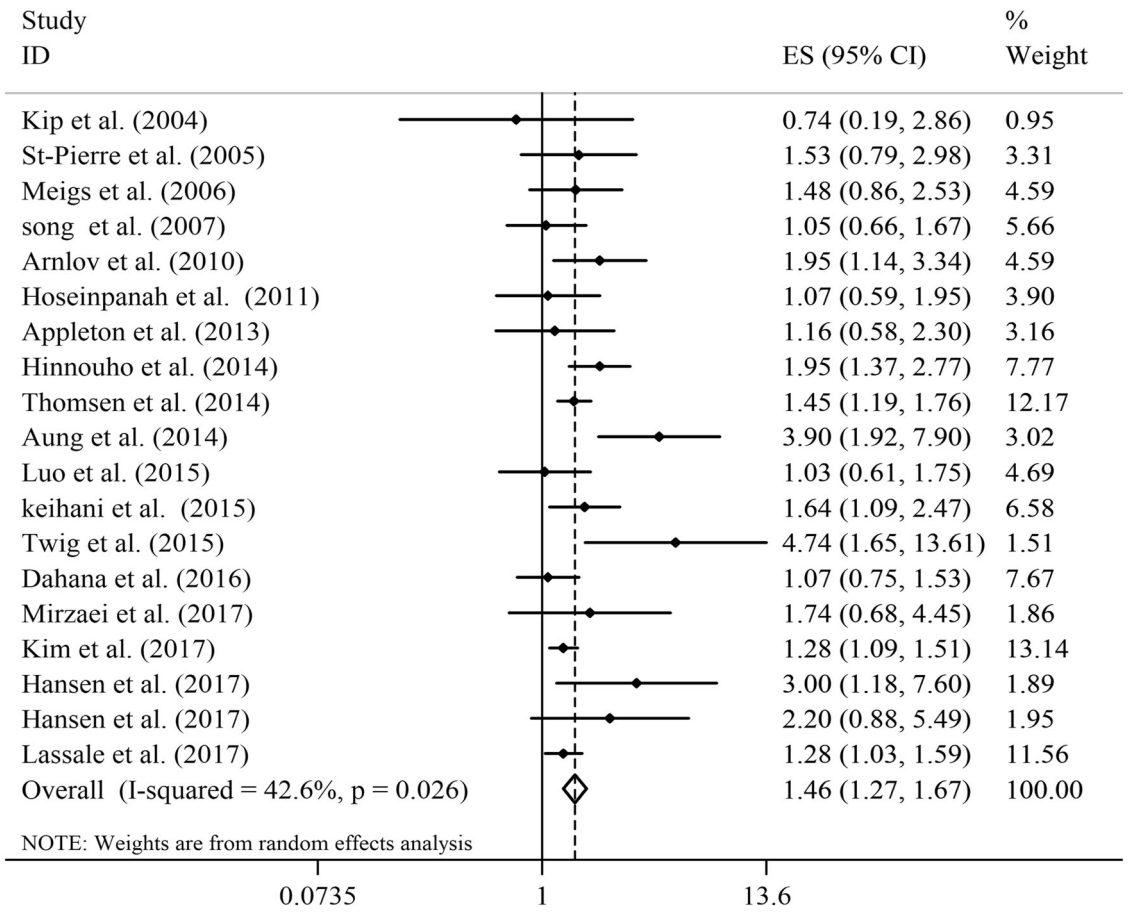

Fig. 8 Forest plot for the association between metabolically healthy obese phenotypes and the risk of cardiovascular diseases using a random-effects model

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Author contributions A.M. and S.S.-B. contributed to the study concept and design; H.M. and A.B. designed search strategy and screened papers. A.B., S.S.-B. and K.D. performed statistical analysis; A.M. wrote the first draft of manuscript; all authors read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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