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Associations between metabolic phenotypes and diabetes risk: A systematic review and meta-analysis

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ABSTRACT

Introduction: It seems that the risk of developing diabetes cannot be predicted solely based on weight or BMI. Metabolic phenotypes might offer a more precise tool for identifying patients at higher risk of diabetes, thus enabling more effective and targeted preventive interventions.
Objective: To determine the association between these metabolic phenotypes and the risk of diabetes.
Materials: Systematic Review (SR) with a meta-analysis of cohort studies. The search was carried out in four databases: Pubmed/Medline, SCOPUS, Web of Science, and EMBASE. Metabolic states were classified into six groups: Metabolically Healthy Normal Weight (MHNW), Metabolically Unhealthy Normal Weight (MUNW), Metabolically Healthy Overweight (MHOW), Metabolically Unhealthy Overweight (MUOW), Metabolically Healthy Obesity (MHO), and Metabolically Unhealthy Obesity (MUO). Association measures were presented as odds ratios (OR) and hazard ratios (HR) along with their 95 % confidence intervals (CI95%).
Results: A total of six studies were evaluated. For the meta-analysis, only studies using OR as the measure of association were included. Compared with individuals with MHNW, a statistically significant association was found for MUNW (OR: 1.82; CI95% 1.62, 2.04), MHOW (OR: 1.19; CI95% 1.07, 1.32), MUOW (OR: 2.44; CI95% 2.19, 2.72), MHO (OR: 2.14; CI95% 1.52, 3.01), and MUO (OR: 3.94; CI95% 3.28, 4.74).
Conclusions: Metabolic phenotypes are significantly associated with the risk of diabetes, regardless of BMI. Further research in this field is required, and should be conducted in other regions of the world where obesity and diabetes rates are rapidly increasing.

1. Introduction

Diabetes, a chronic disease, occurs when the pancreas does not produce enough insulin or when the body cannot effectively utilize it. This condition can lead to hyperglycemia, a characteristic manifestation of this disease (Diabetes Canada Clinical Practice Guidelines Expert Committee et al., 2018).

The global prevalence of diabetes in adults has steadily increased. It is estimated that there are 425 million people affected, according to the International Diabetes Federation. This figure could rise to 629 million by 2045 if preventive measures are not taken (Cho et al., 2018). The prevalence in China is 11.6 % (Xu et al., 2013), and in the United States, it's 9 % (Menke et al., 2015). Within Europe, diabetes is found in 1 out of every 11 adults, with estimates showing a rise to 67 million influenced people by the year 2030 (Home et al., 2022). It is thought that over one-third (36 %) of grownups living with diabetes remain undiscovered. An investigation on diabetes mellitus directed in Spain and distributed in 2012 assessed that somewhere in the range of 14 % of the grown-up populace is influenced by this condition (Rojo-Martínez et al., 2020).

For type 2 diabetes, one of the risk factors, measured by body mass

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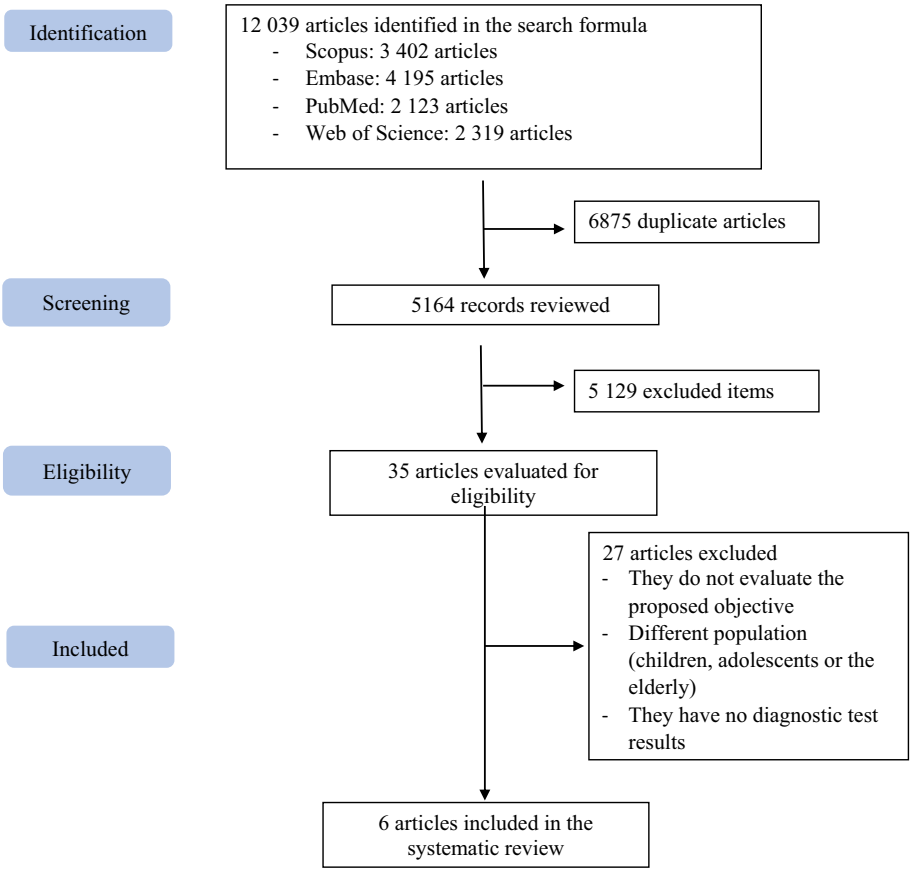


Fig. 1. Flowchart.

index (BMI), is obesity (Verma and Hussain, 2017). However, not all obese individuals develop diabetes, and conversely, not all patients with diabetes are obese. Observing this, researchers have identified various "metabolic phenotypes" that describe variability in metabolic risk among patients of different body sizes (Aung et al., 2014; Janghorbani et al., 2017; Kim et al., 2016; Natarajan et al., 2021; Ryoo et al., 2015; Xu et al., 2021).

Thus, it appears that the risk of developing diabetes cannot be predicted solely by weight or BMI. Metabolic phenotypes may provide a more precise tool for identifying patients at higher risk of diabetes, such as the metabolically unhealthy lean and the metabolically unhealthy obese states (Aung et al., 2014; Janghorbani et al., 2017), enabling more effective and targeted preventive interventions (Wang et al., 2011). This systematic review and meta-analysis aims to provide a comprehensive view of the association between these metabolic phenotypes and the risk of diabetes.

2. Methods

This is a systematic review (SR) with a meta-analysis of cohort studies. We adhered to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement for reporting the structure of this study (Moher et al., 2009).

2.1. Search strategy

For this study, we used search strategies in four databases: Pubmed/Medline, SCOPUS, Web of Science, and EMBASE. Key search terms "metabolic phenotype" and "diabetes" were used. The specific search strategies employed for each database are available in Supplementary Material 1.

2.2. Selection criteria

Studies were considered eligible for this meta-analysis if they met the following criteria: 1) had a cohort design; 2) analyzed the relationship of metabolically healthy (MH) and metabolically unhealthy (MU) phenotypes; 3) stratified by body mass index; 3) included people aged 18 years or older; 4) reported hazard ratio (HR), relative risk (RR), or odds ratio (OR) for evaluating the incidence of diabetes; 4) if diabetes was measured by any of the criteria established by the American Diabetes Association (ADA); 5) Studies that were carried out between the period 2000 to 2023. Research works were excluded if: 1) they were letters to the editor or conference proceedings abstracts, protocols, and review studies; 2) articles that did not provide inferential statistics and measures of association; 3) articles without an abstract and full text in Spanish or English.

Metabolic states were classified into six groups: metabolically healthy normal weight (MHNW), metabolically unhealthy normal weight (MUNW), metabolically healthy overweight (MHOW), metabolically unhealthy overweight (MUOW), metabolically healthy obesity (MHO), and metabolically unhealthy obesity (MUO). If the terminology varied among the studies, it was standardized according to these denominations. Moreover, it was not a strict requirement that all studies adopted identical cut-off points to define normal weight, overweight, and obesity, nor was the same criteria strictly imposed for "metabolically unhealthy". This allowed the inclusion of a wider range of studies in our analysis.

Diabetes was defined as fasting glucose alteration according to the definition criteria of the American Diabetes Association (ADA), Fasting plasma glucose (FPG) $\geq$ 7.0 mmol/L ($\geq$126 mg/dL) (Wang et al., 2011), 2-h plasma glucose $\geq$11.1 mmol/L ($\geq$200 mg/dL) (Wang et al., 2011), or elevated Hemoglobin A1c (HbA1c) ($\geq$6.5 %) (American Diabetes

Table 1
Description of the studies included in the systematic review.

First author, year	Country	Follow up time (mean or median)	Sample	Population (selection criteria)	Sex (% female)	Mean (SD) or median (ICR) age	Definition of obesity	Definition of metabolic unhealthy	Incidence of diabetes (%)	Diagnostic criteria for diabetes	Association measure	Adjustment variables
Aung, 2013	USA	7.4 years	5158	Aged 25 to 64 years Mexican American and non-Hispanic White men and nonpregnant women	59.92 %	MHNW: 39.8 (0.3) MUNW: 46.1 (0.8) MHOW: 42.0 (0.3) MUOW: 45.9 (0.5) MHO: 41.8 (0.5) MUO: 44.2 (0.5)	Normal weight (<25 kg/m2) Overweight (25–29.9 kg/m2) Obesity (≥30 kg/m2)	Wildman criteria, except for high-sensitivity C-reactive protein	MHNW: 1.9 % MUNW: 8.1 % MHOW: 4.6 % MUOW: 17.8 % MHO: 9.4 % MUO: 30.5 %	Fasting glucose ≥126 mg/dL and/or2-h glucose ≥200 mg/dL	Odds ratio MHNW: Reference MUNW: 2.5 (1.1–5.6) MHOW: 1.8 (1–0 - 3.4) MUOW: 5.8 (3.2–10.4) MHO: 3.9 (2.0–7.4) MUO: 10.9 (6.2–19.2)	Adjusted for age, sex, ethnic origin, family history of DM, and fasting glucose
Janghorbani, 2017	Iran	10.1 years	1982	Aged 30 to 70 years People with type 1 and 2 diabetes, and if not attend follow-up examinations	74.77 %	43.0 (6.5)	Normal weight (<25 kg/m2) Overweight (25–29.9 kg/m2) Obesity (≥30 kg/m2)	The third report of the National Cholesterol Education Program Adult Treatment Panel III (NCEPATP III) criteria	MHNW: 7.5 % MUNW: 12.9 % MHOW: 5.4 % MUOW: 18.9 % MHO: 18.4 % MUO: 24.2 %	≥126 mg/dL or a post 2-h glucose after the 75-g OGTT (2hPG) of 200 mg/dL	Odds ratio MHNW: Reference MUNW: 1.79 (0.71–4.49) MHOW: 0.73 (0.24–2.27) MUOW: 2.75 (1.17–6.45) MHO: 2.96 (1.07–8.24) MUO: 3.86 (1.64–9.11)	Adjusted for age and gender
Kim, 2016	Korean	7.7 years	7588	Aged 40 to 69 years Were excluded subjects with diabetes at baseline exam, previous history of cardiovascular disease, or missing information about diabetes or cvd or metabolic health status	66.43 %	MHNW: 50.6 (8.8) MUNW: 49.9 (7.9) MHO: 53.8 (9.2) MUO: 52.2 (7.9)	Normal weight (<25 kg/m2) Obesity (≥25 kg/m2)	Presence/absence of ≥2 components of metabolic syndrome using the NCEP ATP III criteria, except abdominal obesity	MHNW: 7.7 % MUNW: 23.4 % MHO: 9.8 % MUO: 28.7 %	≥126 mg/dL or a post 2-h glucose after the 75-g OGTT (2hPG) of 200 mg/dL	Hazard ratio MHNW: Reference MUNW: 3 (2.5–3.6) MHO: 1.2 (0.99–1.60) MUO: 4 (3.4–4.7)	Adjusted for age, sex, study site, exercise habits, smoking status, and alcohol intake.
Natarajan, 2021	India	9.1 years	1368	Aged ≥20 years Were excluyed subjects with diabetes at baseline examen	58.11 %	40	Normal weight (<25 kg/m2) Obesity (≥25 kg/m2)	≥2 components of metabolic syndrome according to the 2009 International Diabetes Federation consensus criteria	MHNO: 15.9 % MUNW/MONO: 41.3 % MHO: 27.1 % MUO/MOO: 45.1 %	FSG ≥ 126 mg/dL or a post 2-h glucose after the 75-g OGTT (2hPG) of 200 mg/dL	Hazard ratio MHNO/MHNO: Reference MUNW/MONO: 2.44 (2.23–3.80) MHO: 1.61 (1.16–2.23) MUO/MOO: 2.99 (1.79–3.33)	Adjusted for age, gender, family history of diabetes, physical activity, smoking and alcohol use
Ryoo, 2015	Korean	5 years	31,834	Korean men A large group of men were omitted from the study due to factors that could potentially influence	0.00 %	43.0 ± (7.2)	Normal weight (<25 kg/m2) Overweight (25–29.9 kg/	≥2 components metabolic abnormalities among the four components of metabolic syndrome	MHNW: 6.3 % MUNW: 11.8 % MHOW:	FSG ≥ 126 mg/dL or HbA1c ≥ 6.5 %	Odds ratio MHNW: Reference MUNW: 1.81 (1.61–2.04)	Adjusted for age, triglyceride, GGT, eGFR, smoking status, alcohol intake, regular

(*continued on next page*)

Table 1 (*continued*)

First author, year	Country	Follow up time (mean or median)	Sample	Population (selection criteria)	Sex (% female)	Mean (SD) or median (ICR) age	Definition of obesity	Definition of metabolic unhealthy	Incidence of diabetes (%)	Diagnostic criteria for diabetes	Association measure	Adjustment variables
				diabetes development or metabolic health. These exclusion factors included a history of cancer or cardiovascular disease, being underweight, missing metabolic syndrome data, lacking insulin resistance information, absence baseline diabetes records, and having diabetes at the outset of the study.			m2) Obesity (≥30 kg/m2)	besides waist circumference criteria plus insulin resistance status defined by HOMA-IR	7.5 % MUOW: 14.9 % MHO: 9.2 % MUO: 20.1 %		MHOW: 1.18 (1.06–1.32) MUOW: 2.36 (2.11–2.63) MHO: 1.58 (1.03–2.41) MUO: 3.47 (2.84–4.24)	exercise, and hypertension
Xu, 2021	China	9 years	1128	Adults ≥20 years were selected using stratified sampling methods according to the sex and age distribution	57.70 %	41.66	Normal weight (<254 kg/m2) Overweight (25–29.9 kg/m2) Obesity (≥30 kg/m2)	Excess Body fat percentage (≥24 % in men; ≥33 % in women)	MHNW: 6.3 % MUNW: 11.8 % MHOW: 7.5 % MUOW: 14.9 % MHO: 9.2 % MUO: 20.1 %	Use of antidiabetic medications, a fasting glucose level ≥ 7.0 mmol/l, or a 2-h glucose level ≥ 11.1 mmol/l after a 75 g OGTT	Hazard ratio MHNW: Reference NWO/MUNW: 2.110 (1.026–4.337) OWNO/ MHOW: 0.441 (0.101–1.928) OWO/MUOW: 3.465 (2.163–5.551)	Adjusted for age, (gender), cigarette smoking, alcohol drinking, physical activities, family history of diabetes and baseline blood glucose levels

Association, 2022).

2.3. Study selection

The software Rayyan (https://rayyan.qcri.org) was used to save the articles found in each of the explored databases. Three researchers independently reviewed the titles and abstracts of the manuscripts. If both agreed that a manuscript should be included, it was; otherwise, it was excluded. In case of discrepancy, co-authors met to reach a consensus on that manuscript.

Subsequently, we proceeded to review the full text of all included articles. In an-Excel sheet, it was noted whether the study should be included or not. This procedure was carried out in the same way as the previous process.

2.4. Data extraction and qualitative analysis

The remaining articles were subjected to data extraction, through a card in Microsoft Excel 2022. The following information was extracted from each selected article: first author, year, country, design, follow-up time, sample, population (selection criterion), sex (% female), age in mean (SD) or median (IQR), definition of obesity, definition of metabolically unhealthy, incidence of diabetes, diagnostic criterion for diabetes, measure of association, adjustment variables.

2.5. Risk of bias assessment

Three evaluators independently examined the risk of bias in each of the selected studies and debated their findings until reaching an agreement. The New Castle Ottawa (NCO) risk of bias tool for cohorts was used for this purpose (Ottawa Hospital Research Institute, 2022). Briefly, the NCO evaluates the risk level of a manuscript based on three main criteria: 1) study selection: assessing the sample representativeness, selection of the non-exposed, and confirmation of the exposure; 2) comparability: considers whether the researchers have adequately controlled confounding factors in the study design or analysis; 3) outcomes: evaluates how the outcomes were assessed, how long participants were followed, and whether losses during follow-up were considered. Each criterion is evaluated according to a series of subcriteria, and studies receive stars for complying with these subcriteria. Studies with ≥7 stars were considered to have a low risk of bias.

2.6. Quantitative analysis

Analyses were performed with RevMan 5.3. The variables of interest were worked on in a dichotomized manner. The resulting variable was prediabetes, while the dependent variable was obesity. Measures of association were presented as odds ratios (OR) together with their 95 % confidence intervals (CI 95 %).

Cochrane Q test and the estimation of the I2 statistic were used to evaluate heterogeneity among the included cohort studies (Higgins and Thompson, 2002). Significant heterogeneity was considered if I2 > 50 % (https://training.cochrane.org/handbook, 2021). Due to heterogeneity, results were reported through the DerSimonian and Laird fixed effects models.

2.7. Ethical considerations

This study is a secondary analysis of primary studies published in scientific journals, so the risks to the people who formed part of the studies are minimal.

Table 2
Assessment of the quality of the included studies using the Newcastle-Ottawa scale for cohort studies.

Authors, year	Selection				Comparability		Outcome			Score	Overall judgement
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Exposure ascertainment	Outcome not present at the start of the study	Study controls for sex and age	Study controls for any additional important factor	Assessment of outcome	Length of follow-up	Adequacy of follow up		
Aung, 2013	*	*	*	*	*	*	*	*	*	9	Low risk
Janghorbani, 2017	*	*	*	*	*		*	*		7	Low risk
Kim, 2016	*	*	*	*	*	*	*	*	*	9	Low risk
Natarajan, 2021	*	*	*	*	*	*	*	*		8	Low risk
Ryoo, 2015	*	*	*	*	*	*	*	*		8	Low risk
Xu, 2021	*	*	*	*	*	*	*	*		8	Low risk

3. Results

3.1. Eligible studies

A total of 12,039 publications were identified. Duplicates were eliminated (6875), and a total of 5164 manuscripts were evaluated by title and abstract. Subsequently, 5129 research papers were excluded, leaving 35 manuscripts, which were evaluated in full text. Finally, after applying the selection criteria, six articles were obtained (Aung et al., 2014; Janghorbani et al., 2017; Kim et al., 2016; Natarajan et al., 2021; Ryoo et al., 2015; Xu et al., 2021). Fig. 1.

3.2. Characteristics of the studies

All selected manuscripts had a cohort design. The development time of these ranged from 2013 to 2021. These were carried out in five countries: the United States ($n = 1$) (Aung et al., 2014), Iran (n = 1) (Janghorbani et al., 2017), Korea ($n = 2$) (Kim et al., 2016; Ryoo et al., 2015), India (n = 1) (Natarajan et al., 2021) and Xu (Xu et al., 2021). The total number of participants reached 17,224, ranging from 1368 to 31,834.

The average follow-up time varied from 5 to 10.1 years. All studies included males and females, except for the study by Ryoo et al. (Ryoo et al., 2015), which included only men, while the average age was around 40 years.

The definition of normal weight, overweight, and obesity states was standardized in almost all studies, meeting the classical criterion of <25 kg/m2, 25–29.9 kg/m2, and ≥30 kg/m2, respectively. However, in the work of Kim et al. (Kim et al., 2016) and Natarajan et al. (Natarajan et al., 2021), they were classified as normal weight (<25 kg/m2) versus obesity (≥25 kg/m2).

For the definition of metabolically unhealthy, this was different and used from Wildman's criteria (except for the use of C-reactive protein) (Aung et al., 2014), if three or more markers were met (Janghorbani et al., 2017) or two or more criteria (Kim et al., 2016) of the third report of the National Cholesterol Education Program Adult Treatment Panel III (ATPIII), more than two components or more according to the 2009 International Diabetes Federation consensus criterion (IDF). On the other hand, in the work of Xu et al. (Xu et al., 2021), the excess percentage of fat was used as a criterion.

For the diagnosis of diabetes, the manuscripts were based on the diagnosis based on IFG, IGT and/or HbA1c. The incidence of this disease varied by metabolic state, and was lower in those presenting with MHWN (from 1.9 % to 15.8 %) and higher in MUO (20.1 % to 45.1 %) (Table 1).

3.3. Risk of bias assessment

In general, the risk of bias was low for all evaluated studies. All manuscripts were adjusted for a significant number of variables, except for Janghorbani et al., (Janghorbani et al., 2017) who only did so for age and sex. However, only two studies (Aung et al., 2014; Kim et al., 2016) had a high proportion of the initial participants completing the study (Table 2).

3.4. Meta-analysis of the association between obesity and prediabetes

For the meta-analysis, only studies that used the OR as a measure of association were included. Compared with individuals with MHNW, a statistically significant association was found for NHUW (OR: 1.82; 95 % CI 1.62, 2.04); MHOW (OR: 1.19; 95 % CI 1.07, 1.32); MUOW (OR: 2.44; 95 % CI 2.19, 2.72); MHO (OR: 2.14; 95 % CI 1.52, 3.01); and MUO (OR: 3.94; 95 % CI 3.28, 4.74).

The heterogeneity of the studies, measured through I2, varied from 0 % in the comparison of MHNW and NHUW to 86 % when MHNW versus MUO were compared (Fig. 2).

4. Discussion

In our findings, there is an observed association between metabolic phenotypes and the risk of obesity. Moreover, a greater risk of obesity was found versus the MHNW for NHUW, MHOW, MUOW MHO, MUO. With this, it could be suggested that obesity per se does not absolutely determine the risk for having chronic diseases, such as diabetes mellitus, but rather a person's underlying metabolic profile.

In general, even though conditions, such as overweight and obesity, could pose a slight increase in risk for obesity compared to those with normal weight, their risk continues to be lower than their metabolically unhealthy counterparts. This evidence shows that the body fat indicator alone does not inevitably cause adverse metabolic and health complications. Other factors: chronic inflammation, lipidic alterations, insulin resistance, and the distribution of visceral fat, such as abdominal, appear to be essential risk indicators for the development of metabolic diseases (Gastaldelli et al., 2007; Neeland et al., 2012).

Furthermore, MHO has been found not to be a benign condition, as obese patients had a higher risk of diabetes, besides the metabolic conditions that may or may not be healthy. This emphasizes the importance of continuous surveillance of these users, even if they appear to be metabolically healthy. Simultaneously, the group of individuals with metabolically unhealthy obesity (MUO) presented the highest risk (Aung et al., 2014; Janghorbani et al., 2017; Kim et al., 2016; Natarajan et al., 2021; Ryoo et al., 2015; Xu et al., 2021). This phenotype could present a combination of insulin resistance, dyslipidemia, and chronic inflammation, a combination that could accelerate progress towards

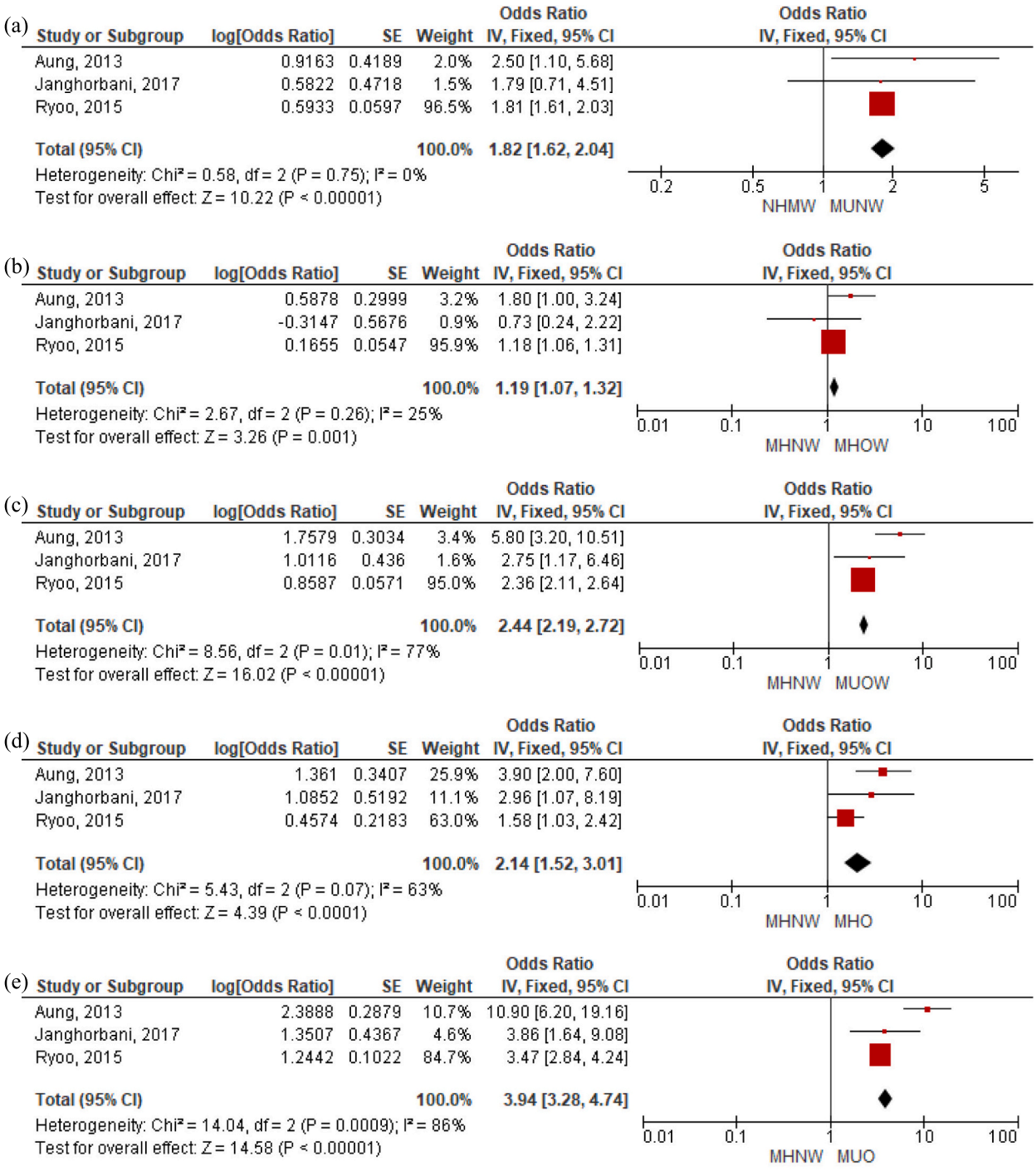


Fig. 2. Metanalysis for the association of MUNW (a), MHOW (b), MUOW (c), MHO (d) and MUO (e) phenotype, compared with individuals with MHNW.

diabetes. This phenomenon is partly explained by the fact that accumulated fat, specifically in the abdomen, can release a variety of pro-inflammatory molecules and hormones that interfere with normal insulin signaling (Kahn et al., 2006; Rosen and Spiegelman, 2014).

Finding a higher risk in the MUOW group is worrying, as this group usually does not receive the necessary clinical attention. These data are supported by the systematic review by Bell et al. (Bell et al., 2014) This highlights the relevance of evaluating metabolic status in those who are overweight, as overweight, apart from obesity, with metabolic dysfunction, can lead to a higher risk of diabetes (Roberson et al., 2014; Hazart et al., 2022).

The criteria used to define metabolic phenotypes varied among the reviewed researches, but were mostly based on establishing the number of cardiometabolic risk factors: dyslipidemia, hypertension, insulin resistance, inflammation, etc. While there is no consensus on the precise definition of the "metabolically unhealthy" state, the results were emphatic in that this group had the highest risk of diabetes versus the MHWN and MHO groups (Aung et al., 2014; Janghorbani et al., 2017; Kim et al., 2016; Natarajan et al., 2021; Ryoo et al., 2015; Xu et al., 2021). From this, it is deduced that the phenotypes that capture the combination of body mass index and cardiometabolic health become useful for risk stratification (Cornier et al., 2011).

The studies included in this review were conducted in the United States, Iran, South Korea, India, and China (Aung et al., 2014;

Janghorbani et al., 2017; Kim et al., 2016; Natarajan et al., 2021; Ryoo et al., 2015; Xu et al., 2021). This implies some geographic representation; it should be highlighted that more studies are needed from Latin America, Africa, and Europe. In Asia, Korean and Indian researches are relevant due to the rapid increase in obesity and diabetes in these places. Asian people tend to present a different body composition and cardiometabolic risk versus Western Europeans. For instance, Asians tend to develop diabetes at a lower body mass index and have more visceral fat for a given body mass index. This indicates how important it is to determine specific cutoff points for users to define obesity, while the Iranian works also provide important information, as rates of obesity and diabetes are rapidly increasing in the Middle East. Therefore, effective interventions are necessary and urgent to address these epidemics in these regions (Crump et al., 2011; Chiu et al., 2011).

It should be noted that visceral fat releases fatty acids and inflammatory adipokines that are the cause of insulin resistance, dysfunction of pancreatic beta cells, and low-grade systemic inflammation. Insulin resistance requires a greater secretion of insulin in order to maintain normoglycemia, which eventually exhausts the beta cells. Chronic inflammation can also directly erode insulin-producing cells. Likewise, ectopic fat deposits in the liver and muscles promote further insulin resistance, which alters the metabolism of these tissues (Pessin and Kwon, 2013; Winer et al., 2011). Visceral fat is also linked to changes in the gut microbiome, such as dysbiosis, which can increase inflammation, intestinal permeability, and insulin resistance. Therefore, adipokines and fatty acids derived from unhealthy abdominal fat deposits can cause endothelial dysfunction, further impairing insulin sensitivity (Castro et al., 2014). Together, these adverse metabolic changes lead to a positive feedback loop, linking excess visceral fat, insulin resistance, inflammation, and beta cell exhaustion; this ultimately culminates in sustained hyperglycemia and clinically apparent type 2 diabetes. Therefore, a comprehensive characterization of obesity phenotypes that include both adiposity and cardiometabolic health is important to establish the risk of this outcome, quite apart from the degree of overweight (Ma et al., 2020).

It is true that our work was the first to measure the relationship between metabolic phenotypes and the risk of diabetes, it had certain limitations; the main one was the heterogeneity among the works, some of which was expected, due to the significant differences between the studies, as there is geographic and methodological diversity; for example, the initial characteristics of the participants, follow-up duration, diagnostic method, and adjustment of confounding factors. Despite this, one should not ignore the fact that there is no standardization in the way to define the metabolically unhealthy state. This heterogeneity may have influenced the results of the meta-analysis and its interpretation. Standardized definitions are necessary to allow more meaningful comparisons between studies (Aung et al., 2014; Janghorbani et al., 2017; Kim et al., 2016; Natarajan et al., 2021; Ryoo et al., 2015; Xu et al., 2021).

Metabolic phenotypes that integrate obesity and markers of cardiometabolic health could help better stratify the risk of type 2 diabetes. The classification of these unhealthy states identifies individuals at higher risk than just using body mass index or other risk factors separately, including not only for diabetes but for other diseases (Gao et al., 2020; Bell et al., 2015). This highlights the importance of considering metabolic health together with excess body fat. At the same time, the early identification of individuals at risk for diabetes is a priority for implementing effective preventive strategies. The results suggest focusing not only on BMI but also on how they are metabolically and how it might have the most significant impact on diabetes prevention (Bell et al., 2014). Intensive lifestyle interventions and, possibly, pharmacotherapy could delay or prevent the onset of diabetes.

5. Conclusions

Our systematic review confirms that metabolic phenotypes are significantly associated with the risk of diabetes, regardless of BMI. The underlying pathophysiological mechanisms, such as insulin resistance, inflammation, and body fat distribution, likely mediate these associations.

More research in this field is needed and should be conducted in other regions of the world, where obesity and diabetes rates are rapidly increasing.

The findings have important implications for clinical practice and public health. They demonstrate the need for more personalized diabetes risk assessments that consider an individual's metabolic profile. Preventive interventions can be adapted according to phenotype to focus on specific physiological targets, such as improving insulin sensitivity and reducing visceral inflammation in metabolically unhealthy phenotypes.

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Authorship contributions

The authors participated in the genesis of the idea, project design, data collection and interpretation, analysis of results, and preparation of the manuscript of this research paper.

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Declaration of competing interest

The authors declare no conflict of interest.

Data availability

No data was used for the research described in the article.

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