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Body composition assessment and future disease risk

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Body composition assessment and future disease risk

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Table of contents

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Editorial: Body composition assessment and future disease risk

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body mass index, obesity, body composition, cohort, bioelectrical impedance

Editorial on the Research Topic
Body composition assessment and future disease risk

Body composition assessment is a fundamental element of chronic disease prevention, diagnosis, and management in clinical practice. Body composition consists of various components, including adipose tissue, muscle mass, bone mass, height, and organ tissues. It is widely used to examine the relationship between these components and health outcomes such as mortality and disease risk. Understanding body composition provides valuable insights into the structure and function of adiposity, the detection of obesity-associated phenotypes, and the mechanisms of chronic disease development (1). Quantifying body composition advances the impact of each component on disease development and management. For instance, body mass index (BMI, kg/m^2) is the most common method to identify obesity and its associated chronic diseases in practice.

Obesity is a critical attribute of many chronic diseases. Obesity is defined as abnormal or excessive body fat associated with chronic disease risk (2). BMI is a rule of thumb for estimating obesity in practice due to its simple and convenient nature. However, although BMI is associated with chronic disease risks, the limitations of BMI have become increasingly apparent in terms of accurately measuring body fat mass and regional fat distribution (3, 4). Additionally, using BMI alone to measure body fat can lead to significant misidentification of patient health risk classification.

A large body of literature has found that overweight or obese individuals defined by BMI sometimes demonstrate better survival and outcomes than normal-weight counterparts (5–7). These studies explain this relationship between BMI and survival by highlighting the inaccuracy of BMI as a measurement of body fat mass. Specifically, some evidence indicates that elevated BMI, an indirect measure of body fat, is not as useful in predicting downstream mortality as a direct measure of body fat (8). Rather, despite a higher BMI, individuals who have more muscle mass and lower lean mass tend to show better outcomes (9, 10). On the other hand, the "skinny fat" or "metabolically obese normal weight (MONW)" body type demonstrates detrimental outcomes among the normal BMI population. However, these body types are neglected in preventive care screening services due to BMI being the standard. Nevertheless, MONW is strongly associated with metabolic syndrome, type 2 diabetes, and cardiovascular disease (CVD) due to the increased workload of the heart and cytokine malfunction (4, 11, 12).

These findings elucidate the need for more effective methods of body composition measurement for better risk assessment of chronic disease morbidity and mortality.

Body composition measurements and chronic diseases

Body composition is strongly associated with chronic diseases. Particularly, adipose tissue is a critical risk factor for obesity associated with chronic diseases (13). As alternative measurements of body composition to BMI have been proposed, such as waist circumference (WC), waist-to-hip ratio (WHR), and direct measures of body fat percentage (BF%) or lean body mass, the relationship between body fat and chronic disease risk extends beyond the conventional approach using BMI.

Visceral fat tissue is directly associated with chronic disease, and the visceral fat index may be an effective measurement to predict the risk of chronic diseases. Huang et al. used the visceral adiposity index (VAI), an indirect measure of visceral body fat combining information from WC, BMI, triglycerides, and HDL cholesterol, to calculate sex-specific visceral fat function. They categorized VAI into quartiles and found a non-linear relationship between VAI and prediabetes and diabetes for both sexes. Especially, they identified a significant threshold at 2.10 for VAI in the early detection of prediabetes and diabetes. If an individual surpasses the 2.10 threshold, they may be at higher risk for developing those conditions.

Utilizing various body composition measurements can enhance the prediction of chronic diseases and hospitalization outcomes more effectively. A meta-analysis analyzed 22 studies on the relationship between WHR and myocardial infarction (MI) over the past 20 years (Zhang et al.). The results demonstrated that a higher WHR is positively associated with MI compared to a lower WHR. Interestingly, gender-specific analysis confirmed this association more specifically, showing that WHR had a stronger association with MI among females. Yan and Chen proved a strong association of four different body composition assessments, including BMI, body fat percentage, WC, and hip circumference, as risk factors for non-suppurative otitis media (NSOM) while the study did not specify the types of NSOM. Of those, hip circumference had the highest association with NSOM. Canonico et al. used calf circumference (CC) to evaluate the risk of in-hospital complication risk and in-hospital mortality. As a result, lower CC was associated with a higher risk of in-hospital complication development and death during hospitalization or within 90 days of discharge in frail older patients (Canonico et al.).

Nutritional intake patterns in children and adolescents show complex relationships with different obesity phenotypes, contributing to our understanding of early risk factors for pediatric chronic diseases. Dietary habits showed a higher association with abdominal obesity measurements such as WC or waist-to-height ratio (WHtR) rather than BMI in children and adolescents aged 6 to 18 years old (Yun et al.). More specifically, those with unhealthy nutritional intake reported three times higher abdominal obesity prevalence compared to those with healthy nutrition intake.

Body composition and adverse outcomes

Reports about an "obesity paradox" exist where higher BMI ranges are protective (14). For example, Li et al. showed a significant association between BMI increments and 29-day mortality in patients with sepsis, indicating that higher BMI is significantly associated with lower mortality. Despite such reports, studies also show that lean mass is a mediator between BMI, adiposity, and patient mortality (9, 15). Therefore, directly measuring body fat may have better utility for measuring outcomes in certain cases. In this regard, Fang et al. found that patients undergoing small cell lung cancer immunotherapy with a higher visceral to subcutaneous fat ratio (VSR) reported a worse response to the therapy than those with a lower VSR. Although unadjusted regression models showed significantly worse overall survival and progression-free survival among patients with sarcopenia or lower skeletal muscle mass compared to those with higher muscle mass, the adjusted models did not show significant outcomes (Fang et al.).

More accurate body composition assessment is particularly important when evaluating older adults experiencing sarcopenia with preserved fat mass. Calf circumference (CC), which serves as a valuable muscle mass marker, was the only significant body composition measurement for all in-hospital mortality, complications, and 90-day mortality compared to hand grip strength and existing clinical frailty among older hospitalized patients (Canonico et al.). Since CC is highly associated with mobility and falls (16), it can provide more valuable insights, demonstrating that age-associated changes in body composition predict adverse outcomes more accurately than static measurements.

Lastly, despite the widespread clinical use of BMI as a cardiovascular disease (CVD) risk factor, there may be limitations when using it with the triglyceride-glucose (TyG) index to capture metabolic risk. More specifically, even though BMI and TyG independently proved to have a significant association with CVD, TyG did not play a role as a mediator of CVD when combined with BMI (Gan et al.).

Body composition assessment evolution

As measurement technology has evolved, more specific body compositions can be measured with a home-based digital scale. However, concerns have been raised about measurement accuracy and usability in practice. Dual-energy X-ray absorptiometry (DXA) scans are the most accurate measurement tool, but they are not easily used in practice and are expensive to use solely for body composition measurement purposes. Bioelectrical impedance analysis (BIA) is an alternative tool that can be used in practice and at home relatively easily. Despite the lower accuracy of BIA compared to DXA scan, its performance is sufficient compared to DXA scan to reliably be used in clinical practice (17–19).

As technology has advanced, new technologies and methodologies have emerged to measure and utilize body composition in predicting health risks. Machine learning is

used to measure comprehensive body composition effectively (20, 21). BF% was generated with a smartphone that uses a three-dimensional scanning application, and the results were reliable compared to DXA scans (Tinsley et al.). It can contribute to assessing multi-dimensional aspects of body composition, from appearance to internal body composition, by utilizing advanced measurement with a smartphone in clinical settings. Furthermore, it may be a more effective, cost-effective way to measure whole body composition for patients.

Clinical implications and conclusion

The growing evidence connecting body composition to chronic disease risk and outcomes has significant implications for clinical practice. Moving beyond the conventional BMI-centric approaches to health assessment allows more precise risk stratification and personalized intervention and care planning. Clinicians can use direct measures of body composition, such as DXA scan or the more clinically utilizable BIA, to identify high-risk patients, such as those with skinny fat or sarcopenic obesity, which might otherwise be missed by using BMI alone.

As body composition and chronic disease research advance, tools and methods directly measuring body composition will become more accurate and reliable. Such tools should be clinically relevant, like BIA, to be valuable in primary care settings where they can enhance early detection of unfavorable body composition and guide preventive intervention before disease develops, ultimately leading to improved patient outcomes and more effective preventive care.

Author contributions

AJ: Writing – review & editing, Writing – original draft. FO: Writing – review & editing, Writing – original draft. AM: Writing – original draft, Writing – review & editing.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Heymsfield SB. Advances in body composition: a 100-year journey. *Int J Obes.* (2024) 20:1–5. doi: 10.1038/s41366-024-01511-9

2. Apovian CM. Obesity: definition, comorbidities, causes, and burden. *Am J Manag Care.* (2016) 22:s176–85.

3. Baumgartner RN, Heymsfield SB, Roche AF. Human body composition and the epidemiology of chronic disease. *Obes Res.* (1995) 3:73–95. doi: 10.1002/j.1550-8528.1995.tb00124.x

4. Nuttall FQ. Body mass index: obesity, BMI, and health: a critical review. *Nutr Today.* (2015) 50:117–28. doi: 10.1097/NT.0000000000000092

5. McAuley PA, Blair SN. Obesity paradoxes. *J Sports Sci.* (2011) 29:773–82. doi: 10.1080/02640414.2011.553965

6. Lavie CJ, McAuley PA, Church TS, Milani RV, Blair SN. Obesity and cardiovascular diseases: implications regarding fitness, fatness, and severity in the obesity paradox. *J Am Coll Cardiol.* (2014) 63:1345–54. doi: 10.1016/j.jacc.2014.01.022

7. Qin J, Zhang T, Chen Y, Wei X, Yang Y, Yuan Y, et al. The effect of body mass index on stroke prognosis: a systematic review and meta-analysis of 32 cohort studies with 330,353 patients. *Int J Stroke.* (2024) 19:1093–101. doi: 10.1177/17474930241255031

8. Mainous AG, Yin L, Wu V, Sharma P, Jenkins B, Saguil AA, et al. Body mass index versus body fat percentage as a predictor of mortality in adults aged 20-49. *Ann Fam Med.* (2024) 22:6079. doi: 10.1370/afm.22.s1.6079

9. Abramowitz MK, Hall CB, Amodu A, Sharma D, Androga L, Hawkins M. Muscle mass, BMI, and mortality among adults in the United States: a population-based cohort study. *PLoS ONE.* (2018) 13:e0194697. doi: 10.1371/journal.pone.0194697

10. Srikanthan P, Horwich TB, Tseng CH. Relation of muscle mass and fat mass to cardiovascular disease mortality. *Am J Cardiol.* (2016) 117:1355–60. doi: 10.1016/j.amjcard.2016.01.033

11. Conway B, Rene A. Obesity as a disease: no lightweight matter. *Obes Rev.* (2004) 5:145–51. doi: 10.1111/j.1467-789X.2004.00144.x

12. Jo A, Mainous III AG. Informational value of percent body fat with body mass index for the risk of abnormal blood glucose: a nationally representative cross-sectional study. *BMJ Open.* (2018) 8:e019200. doi: 10.1136/bmjopen-2017-019200

13. Koenen M, Hill MA, Cohen P, Sowers JR. Obesity, adipose tissue and vascular dysfunction. *Circ Res.* (2021) 128:951–68. doi: 10.1161/CIRCRESAHA.121.318093

14. Flegal KM, Kit BK, Orpana H, Graubard BI. Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. *JAMA.* (2013) 309:71–82. doi: 10.1001/jama.2012.113905

15. Qu Q, Guo Q, Sun J, Lu X, Cheang I, Zhu X, et al. Low lean mass with obesity in older adults with hypertension: prevalence and association with mortality rate. *BMC Geriatr.* (2023) 23:619. doi: 10.1186/s12877-023-04326-x

16. Wei J, Jiao J, Chen CL, Tao WY, Ying YJ, Zhang WW, et al. The association between low calf circumference and mortality: a systematic review and meta-analysis. *Eur Geriatr Med.* (2022) 13:597–609. doi: 10.1007/s41999-021-00603-3

17. Cruz Rivera PN, Goldstein RL, Polak M, Lazzari AA, Moy ML, Wan ES. Performance of bioelectrical impedance analysis compared to dual X-ray absorptiometry (DXA) in veterans with COPD. *Sci Rep.* (2022) 12:1946. doi: 10.1038/s41598-022-05887-4

18. Holmes CJ, Racette SB. The utility of body composition assessment in nutrition and clinical practice: an overview of current methodology. *Nutrients.* (2021) 13:2493. doi: 10.3390/nu13082493

19. Liao YS Li HC, Lu HK, Lai CL, Wang YS, Hsieh KC. Comparison of bioelectrical impedance analysis and dual energy X-ray absorptiometry for total and segmental bone mineral content with a three-compartment model. *Int J Environ Res Public Health.* (2020) 17:2595. doi: 10.3390/ijerph17072595

20. Pleuss JD, Talty K, Morse S, Kuiper P, Scioletti M, Heymsfield SB, et al. machine learning approach relating 3D body scans to body composition in humans. *Eur J Clin Nutr.* (2019) 73:200–8. doi: 10.1038/s41430-018-0337-1

21. Razmpour F, Daryabeygi-Khotbehsara R, Soleimani D, Asgharnezhad H, Shamsi A, Bajestani GS, et al. Application of machine learning in predicting non-alcoholic fatty liver disease using anthropometric and body composition indices. *Sci Rep.* (2023) 13:4942. doi: 10.1038/s41598-023-32129-y

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Obesity and adiposity promote the development of non-suppurative otitis media: a Mendelian randomization study

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Background: Observational studies have found that obesity is associated with the development of non-suppurative otitis media (NSOM), but the causality and pathogenesis are unclear. This study aimed to investigate the association between obesity, lipid metabolism, and NSOM at the genetic level.

Methods: We performed a bidirectional two-sample Mendelian randomization (MR) study to examine the causal relationship between obesity, lipid metabolism-related factors, and NSOM by using the datasets obtained from the IEU Open genome-wide association studies (GWAS) Project. Furthermore, a multivariate MR (MVMR) analysis on lipid indicators was conducted to validate the results. We then used obesity or body mass index (BMI) as the exposure and NSOM as the outcome to search for possible mediators in lipids and adipokines.

Results: Using NSOM as the outcome, we found nine positive exposure results related to obesity and lipid metabolism. Among them, obesity, BMI, body fat percentage, waist circumference, hip circumference, and resistin were risk factors, while apolipoprotein A1 (apoA1), high-density lipoprotein cholesterol (HDL-C), and nerve growth factor (NGF) were protective factors. Then, we used the obesity and lipid metabolism-related factors as outcomes and NSOM as the exposure to perform the MR analysis, which failed to obtain positive results. In the MVMR analysis, we found that HDL cholesterol and apoA1 remained causally associated with NSOM after correction for other potential confounders. Simultaneously, when obesity or BMI was used as the exposure and NSOM as the outcome, HDL cholesterol or apoA1 served as mediators through a two-step MR analysis. The MR analysis for mediation, obesity, and BMI reduced the production of HDL or apoA1, which served as protective factors affecting the development of NSOM.

Conclusion: At the genetic level, obesity and adiposity may promote the development of NSOM, while NSOM has no effect on obesity and adiposity. Obesity can also encourage the progress of NSOM by reducing HDL cholesterol/apoA1. Resistin may be a potential risk factor for NSOM, whereas NGF may be a potential protective factor.

KEYWORDS

obesity, lipid, Mendelian randomization, high-density lipoprotein, apolipoprotein A1

Introduction

Non-suppurative otitis media (NSOM), also known as secretory otitis media, exudative otitis media, serous otitis media, catarrhal otitis media, and tympanic cavity effusion, is a common inflammatory disease of the middle ear. It is usually caused by poor Eustachian tube function and is characterized by otitis media effusion and hearing loss. NSOM is most common in children, and its incidence rate is very high. It usually develops between 6 months and 4 years old (1). In total, 50–90% of children under the age of 5 have a history of NSOM (2). It is also one of the leading causes of hearing loss in children and even has an impact on their intelligence and language development.

Obesity is a global issue of great concern, and it is becoming more serious as living standards rise (3). Obesity has been shown to cause a variety of diseases, including cardiovascular (4) and cerebrovascular disease (5), diabetes (6), obstructive sleep apnea syndrome (7), and metabolic disorders (8). Observational studies have shown that NSOM may be associated with obesity, most of which is concentrated in the pediatric population (9, 10). In addition, observational studies have also found that a high-fat diet rather than obesity is associated with NSOM, and a high-fat diet is a confounding factor between obesity and NSOM (11). At present, the relationship between the two is still not very precise, the mechanism of action and the causal relationship are not clear, and the observational research is easily influenced by confounding factors.

Mendelian randomization (MR) can use genetic instrumental variables to test the potential causal relationship between exposures and outcomes. Because genetic variation occurs randomly and is not influenced by external environmental factors, MR analysis minimizes potential unpredictable confounding factors and compensates for the shortcomings of observational research (12). Cao et al. (13) used MR methods to demonstrate that childhood body mass index is a risk factor for the development of NSOM in children. Considering the correlation between lipid metabolism-related factors and obesity, we also included them in the study and used MR methods to analyze the relationship between obesity, obesity indicators, lipids, adipokines, and NSOM, to gain a preliminary understanding of the disease pathogenesis.

Methods

The exposure and outcome data for MR analysis were collected from the datasets of the IEU Open GWAS Project, and the data on obesity and lipid metabolism were divided into four categories: obesity (phenotype of obesity), obesity indicators, lipids, and adipokines. Obesity indicators include body mass index (BMI), body fat percentage, waist circumference, and hip circumference; lipids include total cholesterol, low-density lipoprotein cholesterol (LDL cholesterol, LDL-C), high-density lipoprotein cholesterol (HDL cholesterol, HDL-C), triglycerides, apolipoprotein A1 (apoA1), and apolipoprotein B (apoB); adipokines include adiponectin, resistin, leptin, agouti-related protein, and nerve growth factor (NGF). There were a total of 16 obesity and lipid metabolism-related GWAS datasets as exposure data. The outcome data were NSOM. The details of the GWAS datasets from the IEU website are shown in Table 1.

To meet the three hypotheses of the MR analysis and minimize the influence of confounding factors, we extracted single nucleotide polymorphisms (SNPs) as instrumental variables that met the following conditions: a clustering window of 10 MB and an r2 cutoff of 0.001. SNPs

TABLE 1 Detailed information on the dataset used in this article from the IEU website.

Category	Traits	PMID	Year	Sample Size	Number of SNPs	Gender	Population
Exposures (obesity)	Obesity	22,484,627	2012	13,848	2,430,514	NA	European
Exposures (obesity indicators)	Body mass index	25,673,413	2015	236,781	2,529,499	NA	European
	Body fat percentage	/	2017	331,117	10,894,596	Males and Females	European
	Waist circumference	34,017,140	2021	407,661	10,783,687	NA	European
	Hip circumference	25,673,412	2015	127,997	2,444,355	Females	European
Exposures (lipids)	Total cholesterol	34,226,706	2021	437,878	4,232,052	NA	European
	LDL cholesterol	34,594,039	2021	343,621	19,037,976	NA	European
	HDL cholesterol	24,097,068	2013	94,595	2,418,527	NA	European
	Triglycerides	32,203,549	2020	441,016	12,321,875	Males and Females	European
	Apolipoprotein A1	35,213,538	2022	115,082	11,590,399	NA	European
	Apolipoprotein B	34,226,706	2021	435,744	4,231,412	NA	European
Exposures (adipokines)	Adiponectin	22,479,202	2012	39,883	2,675,209	Males and Females	Mixed
	Resistin	33,067,605	2020	21,758	13,138,697	NA	European
	Leptin	32,917,775	2020	56,802	231,001	NA	Mixed
	Agouti-related protein	33,067,605	2020	21,758	13,102,571	NA	European
	Nerve growth factor	28,369,058	2018	3,394	5,270,646	Males and Females	European
Outcome	NSOM	/	2021	/	16,380,433	Males and Females	European

GWAS, genome-wide association study; SNP, single nucleotide polymorphisms; LDL, low-density lipoprotein; HDL, high-density lipoprotein; NSOM: non-suppurative otitis media.

associated with every trait were extracted at a significance threshold of $p < 5$ e- 8, but if there were few SNPs extracted for Mendelian randomization, we would reanalyze them at $p < 5e\text{-}6$ or $P<5e\text{-}5$.

In total, 16 datasets related to obesity and lipid metabolism were used as exposures, with NSOM as the outcome. A two-sample MR analysis was performed using MR Egger, weighted media, inverse variance weighted (IVW), simple mode, and weighted mode, in which IVW was used as the main analysis method (referred to as forward MR analysis). If the IVW method produced a *p*-value less than 0.05, a statistically significant causal relationship between exposure and outcome was considered. Additionally, if the odds ratio (OR) >1, risk factors for the development of outcomes were considered; if OR < 1, protective factors were considered. To measure the heterogeneity among SNPs, Cochran's Q test was employed with the MR Egger and IVW methods, and the MR Egger intercept method was used for pleiotropy testing. If the *p*-value of the IVW method was between 0.04 and 0.05, further validation of the sensitivity of the results would be conducted using the "Leave-one-out" analysis, which can remove each SNP one at a time and track how each SNP affects the combined results.

Then, we used NSOM as the exposure and 16 obesity and lipid metabolism-related datasets as the outcomes for a reverse two-sample MR analysis using the MR Egger and IVW methods. There was a statistically significant causal relationship between the outcome and exposure when using the IVW method, with a *p*-value of <0.05. The subsequent validation methods were the same as the forward MR analysis described above.

Due to the interaction between many lipid indicators, we selectively conducted a multivariate MR (MVMR) analysis on lipids to further verify the reliability of the results.

Finally, we employed a two-step MR analysis using the five methods mentioned above, with IVW as the main method. We used obesity and BMI as exposures and NSOM as the outcome to identify potential mediating variables in lipids and adipokines with a causal relationship to NSOM. Both steps used the method of two-sample MR to avoid confounding factors, and SNPs duplicated in the first step were deleted during the second step of the MR analysis. A mediating effect was considered to exist if the *p*-value of both steps in the MR analysis using the IVW method was less than 0.05. We called the total effect value of exposure to outcome "beta all," the effect value of the first step of MR analysis of exposure to the mediator "beta1," the effect value of the second step of MR analysis of mediator to outcome "beta2," the mediator effect value "beta12"(beta1*beta2), the direct effect value of exposure to outcome "beta_dir"(beta all-beta1*beta2), and the ratio of mediator effect "beta_per"(beta1*beta2/beta all).

All data analyses were processed using R 4.3.2 and related extension packages.

Results

Two-sample MR

Forward MR analysis

In total, 16 datasets related to obesity and lipid metabolism were used as exposures, with NSOM as the outcome. SNPs associated with all traits were extracted at a significance threshold of $p < 5$ e- 8. There were a total of nine positive factors, namely, obesity, BMI, body fat percentage, waist circumference, hip circumference, HDL cholesterol, apoA1, resistin, and NGF. Among all positive factors, the direction of action in the results using the five methods was also consistent.

Obesity (phenotype of obesity)

The IVW analysis revealed a causal relationship between obesity and NSOM ($p = 0.02$); the OR value greater than 1 indicated that obesity was a risk factor for NSOM. The Cochran's Q *p*-value and the MR Egger intercept *p*-value were both greater than 0.05, indicating that there was no heterogeneity and pleiotropy in the result.

Obesity indicators

All four obesity indicators were positive exposures, including BMI, body fat percentage, waist circumference, and hip circumference. The OR values for the obesity indicators were all greater than 1, specifically 1.37, 1.30, 1.32, and 2.30, showing that these four indicators were risk factors for the development of NSOM. In the heterogeneity test, all Cochran's *Q* *p*-values were greater than 0.05, indicating that there was no heterogeneity in the results. The MR Egger intercept for all dataset results had *p*-values greater than 0.05, indicating that there was no pleiotropy in the data results (Figure 1).

Lipids

Among the six indicators, HDL-C and apoA1 had a causal relationship with the outcome of NSOM, and their OR values were all less than 1, indicating that they were protective factors against the progression of the disease. In the heterogeneity test, all Cochran's Q *p*-values were greater than 0.05, indicating that there was no heterogeneity in the results. The *p*-values of MR Egger intercept for all results were all greater than 0.05, indicating that there was no horizontal pleiotropy (Figure 2).

Adipokines

Among the five indicators of adiponectin, the *p*-values of resistin and NGF using the IVW analysis method were less than 0.05, indicating that the two were positive exposures. Resistin, with an OR greater than 1, was identified as a pathogenic factor for the progression of the disease, while NGF, with an OR lower than 1, was considered a protective factor against disease progression. According to the data in Figure 3, heterogeneity and horizontal pleiotropy of the two positive exposures can be excluded. The "Leave-one-out" analysis of susceptibility shows that the MR test was reliable (Figure 4).

Reverse Mendelian randomization analysis

Using the 16 obesity- and lipid metabolism-related factors as outcomes and NSOM as the exposure, the MR analysis was performed using the IVW and MR Egger methods, and it was found that all datasets had no positive results. The *p*-values of all IVW analysis results were greater than 0.05. To obtain sufficient instrumental variables, we set the threshold for extracting significant SNPs to $p < 5e\text{-}6$, except for acting leptin as the outcome to $p < 5e\text{-}5$. Although the *p*-value of Cochran's *Q* test for several data was less than 0.05, it may be because the data came from different analysis platforms, experiments, and populations. There was no pleiotropy in the data results, as indicated by *p*-values larger than 0.05 for the MR Egger intercept for all dataset outcomes (Supplementary Table S1).

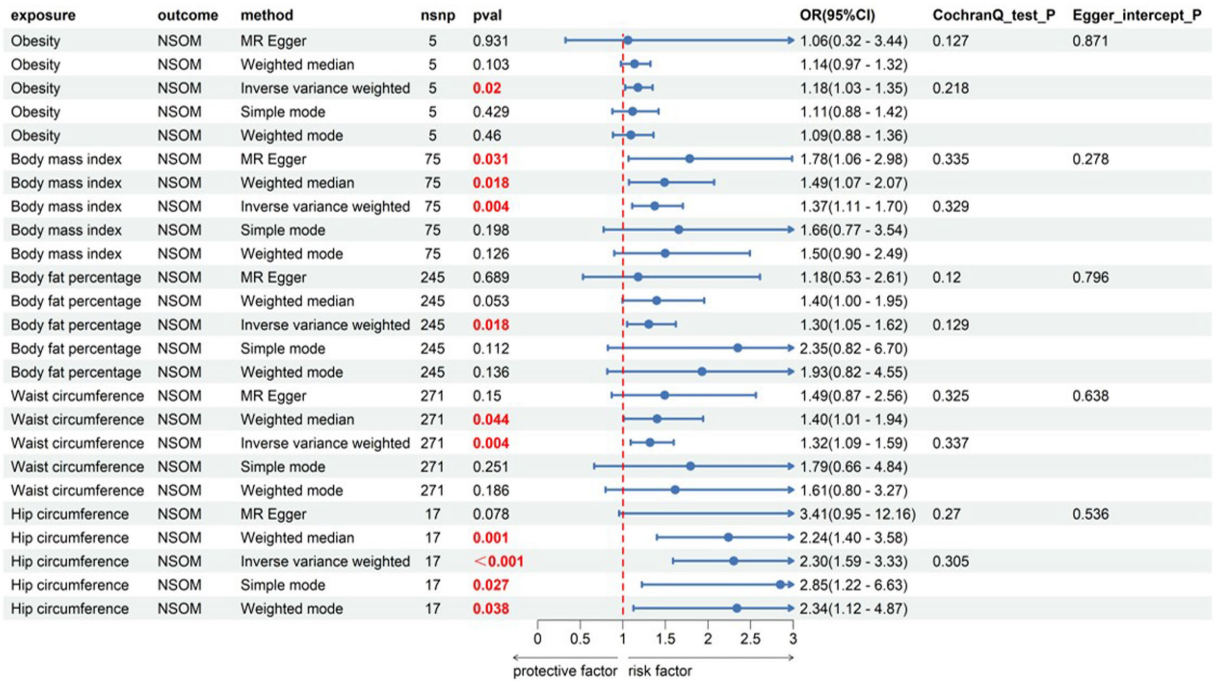


FIGURE 1
Forward Mendelian randomization analysis data on obesity, obesity indicator, and NSOM. The red text denotes the *p*-value for this trait is less than 0.05. nsnp, number of single nucleotide polymorphisms used as instrumental variables for Mendelian randomization; OR, odds ratio; CI, confidence interval; NSOM, non-suppurative otitis media.

MVMR

Combining the positive results obtained in the two-sample MR analysis, we grouped HDL-C, LDL-C, and triglycerides into one group and apoA1 and apoB into another group. By correcting for the effects of LDL-C and triglycerides on NSOM, the causal effect of HDL-C on NSOM remained significant. By correcting for the effects of apoB on NSOM, the causal effect of apoA1 on NSOM also remained significant (Figure 5).

Two-step MR

In the two-sample MR analysis, we obtained four lipid metabolism-related factors causally associated with NSOM: HDL-C, apoA1, resistin, and NGF. In the two-step MR analysis, we used these four datasets as a suspected mediator and set the threshold for extracting significant SNPs to $p < 5e\text{-}8$. The analysis revealed that HDL and apoA1 could serve as mediators when using obesity as an exposure (Figure 6). The mediation effects were 0.016 and 0.01, respectively, and the percentage of the mediation effects was 0.099 and 0.063, respectively. HDL and apoA1 can also be used as mediators when using the BMI as the exposure (Figure 7); the mediation effects were 0.05 and 0.041, respectively, and the percentage of the mediation effects was 0.158 and 0.13, respectively. The direction of action with the MR Egger method was different from the other four methods when using obesity as the exposure and apoA1 as the outcome; except for the above, the direction of the results using the five methods used for MR was consistent. The *p*-value of the MR Egger intercept was greater than 0.05 for all analyzed procedures, indicating that there was no pleiotropy (Supplementary Table S2) (Table 2).

Discussion

In this study, we used an MR method of multi-factors to explore the genetic impact of obesity, obesity indicators, lipids, and adipokines on the risk of NSOM. We aimed to explore the potential factors and pathogenesis of NSOM related to obesity and lipid metabolism and strived to find new treatments, thereby reducing the incidence rate of NSOM and improving its prognosis. We used five methods in MR analysis, namely MR Egger, weighted media, IVW, simple mode, and weighted mode. Although many results showed inconsistent MR estimates, considering the advantage of IVW in maintaining higher estimation accuracy (14), if the *p*-value of IVW was less than 0.05, we believed that there was a statistically significant causal relationship between exposure and outcome. In this MR analysis, a total of nine factors of obesity and lipid metabolism were found to have a causal relationship with the risk of NSOM, which is consistent with the conclusion drawn from observational studies that obesity may affect the development of NSOM and provides a theoretical basis for its related pathogenesis.

This study found that obesity and four obesity-related indicators, namely obesity, BMI, body fat percentage, waist circumference, and hip circumference, all increase the risk of NSOM, indicating that obesity and increased body fat were risk factors for NSOM. In observational studies, the BMI of children with NSOM was significantly higher than that of normal children (9, 10, 15). Kim et al. found that 21.4% of children with NSOM were overweight and 17.8% were obese, with a higher prevalence of obesity in the study group than in the control group (10.5%) (16). Interestingly, a study from

exposure	outcome	method	nsnp	pval	OR(95%CI)	CochranQ_test_P	Egger_intercept_P
Total cholesterol	NSOM	MR Egger	193	0.59	0.96(0.81 - 1.13)	0.174	0.99
Total cholesterol	NSOM	Weighted median	193	0.713	0.96(0.77 - 1.19)		
Total cholesterol	NSOM	Inverse variance weighted	193	0.435	0.95(0.85 - 1.07)	0.187	
Total cholesterol	NSOM	Simple mode	193	0.402	0.82(0.52 - 1.30)		
Total cholesterol	NSOM	Weighted mode	193	0.513	0.95(0.81 - 1.11)		
LDL cholesterol	NSOM	MR Egger	158	0.825	0.98(0.84 - 1.15)	0.055	0.843
LDL cholesterol	NSOM	Weighted median	158	0.778	0.97(0.81 - 1.17)		
LDL cholesterol	NSOM	Inverse variance weighted	158	0.645	0.97(0.86 - 1.09)	0.062	
LDL cholesterol	NSOM	Simple mode	158	0.341	0.80(0.51 - 1.26)		
LDL cholesterol	NSOM	Weighted mode	158	0.755	0.98(0.84 - 1.14)		
HDL cholesterol	NSOM	MR Egger	86	0.12	0.85(0.70 - 1.04)	0.059	0.502
HDL cholesterol	NSOM	Weighted median	86	**0.02**	0.80(0.66 - 0.96)		
HDL cholesterol	NSOM	Inverse variance weighted	86	**0.001**	0.81(0.71 - 0.91)	0.063	
HDL cholesterol	NSOM	Simple mode	86	**0.013**	0.61(0.41 - 0.89)		
HDL cholesterol	NSOM	Weighted mode	86	**0.015**	0.81(0.69 - 0.96)		
Triglycerides	NSOM	MR Egger	284	0.297	1.09(0.92 - 1.29)	0.049	0.959
Triglycerides	NSOM	Weighted median	284	0.177	1.13(0.95 - 1.35)		
Triglycerides	NSOM	Inverse variance weighted	284	0.109	1.10(0.98 - 1.23)	0.053	
Triglycerides	NSOM	Simple mode	284	0.491	0.87(0.58 - 1.30)		
Triglycerides	NSOM	Weighted mode	284	0.476	1.06(0.90 - 1.25)		
Apolipoprotein A1	NSOM	MR Egger	69	**0.049**	0.80(0.64 - 0.99)	0.359	0.972
Apolipoprotein A1	NSOM	Weighted median	69	**0.002**	0.73(0.59 - 0.89)		
Apolipoprotein A1	NSOM	Inverse variance weighted	69	**<0.001**	0.80(0.70 - 0.90)	0.391	
Apolipoprotein A1	NSOM	Simple mode	69	**0.013**	0.61(0.42 - 0.89)		
Apolipoprotein A1	NSOM	Weighted mode	69	**0.004**	0.73(0.59 - 0.90)		
Apolipoprotein B	NSOM	MR Egger	183	0.984	1.00(0.88 - 1.13)	0.048	0.487
Apolipoprotein B	NSOM	Weighted median	183	0.765	0.98(0.85 - 1.13)		
Apolipoprotein B	NSOM	Inverse variance weighted	183	0.629	1.02(0.93 - 1.14)	0.05	
Apolipoprotein B	NSOM	Simple mode	183	0.277	0.76(0.47 - 1.24)		
Apolipoprotein B	NSOM	Weighted mode	183	0.822	0.98(0.87 - 1.12)		

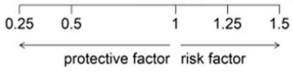


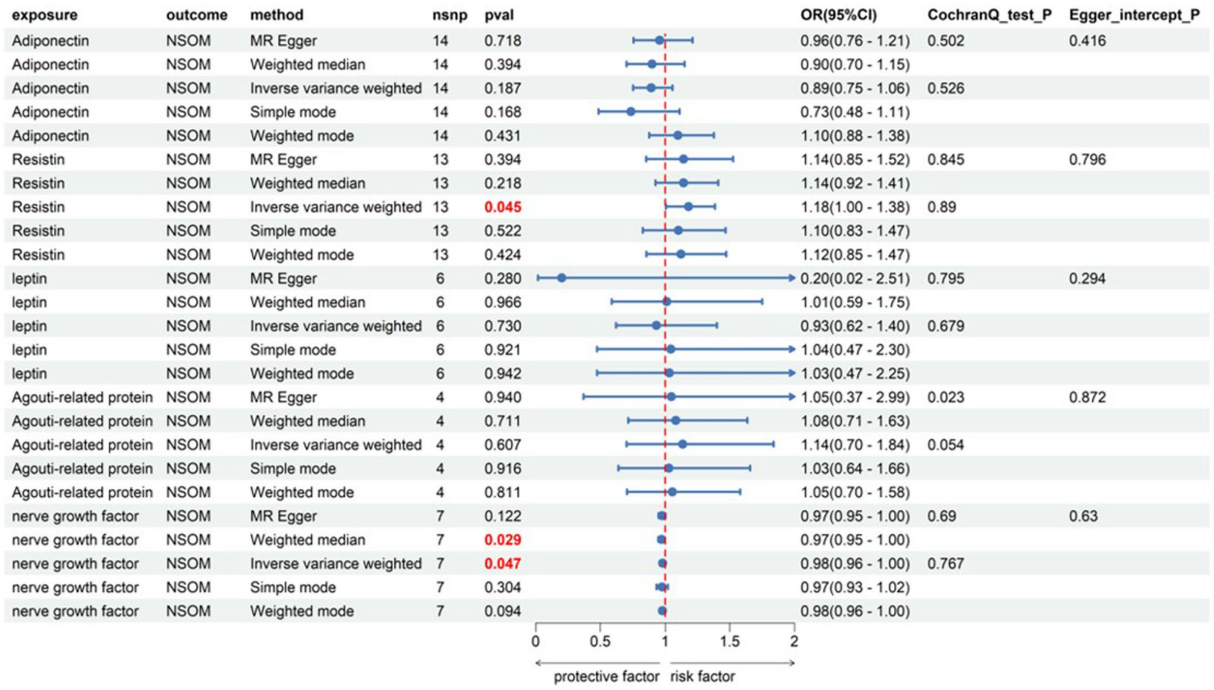
FIGURE 2
Forward Mendelian randomization analysis data on lipids and NSOM. The red text denotes that the *p*-value for this trait is less than 0.05.nsnp, number of single nucleotide polymorphisms used as instrumental variables for NSOM, non-suppurative otitis media.

Korea showed that fat intake, but not BMI, was associated with NSOM (11). Specifically, in the healthy weight group, higher fat intake was associated with a higher risk of NSOM. Unfortunately, our study did not determine whether BMI or fat contributed more to NSOM. More research may be needed to confirm this.

It is well known that adenoid hypertrophy leads to NSOM. One study (17) has shown that children with chronic NSOM have a higher incidence of overweight or obesity, and the presence and degree of adenoid or tonsil hypertrophy are not related to overweight or obesity, which indirectly suggests that tonsil and adenoid hypertrophy are not confounders between obesity and NSOM. Normal Eustachian tube function is the foundation for maintaining the normal function of the middle ear. Obese patients may alter the structure of the fat tissue around the Eustachian tube by altering its accumulation, thereby affecting Eustachian tube function and making NSOM more likely to occur (18). In addition, obesity is often associated with obstructive sleep apnea–hypopnea syndrome, which can lead to increased intra-abdominal pressure, decreased intrathoracic pressure, and exacerbation of gastroesophageal reflux (19). Reflux can cause damage to the mucosa of the Eustachian tube and tympanic cavity, thereby exacerbating the occurrence of NSOM. Therefore, changes in tube function and gastroesophageal reflux may be intermediate variables between obesity and NSOM.

For children, there is no gender difference in the incidence of NSOM, although NSOM is most common under the age of 2 and reaches another peak at the age of 5 (20). Gender and age are key factors for BMI (21, 22), which can be used to assess the greatest association between overweight and body fat and is widely used to measure obesity (23). To date, there is insufficient evidence for gender and age distribution differences in the higher BMI of NSOM patients than healthy children. Mehmet et al. (10) found that after grouping by gender, BMI remained statistically significantly higher in NSOM patients against controls in both boys and girls. They also found no difference in BMI between the NSOM and control groups at age (6, 8 for boys and 6, 9, 10, 11 for girls); however, the percentile range of BMI was higher in the NSOM group.

There are few reports about lipids related to NSOM. It has been reported that serum total cholesterol in the NSOM group is significantly higher than that in the controls, while triglycerides are not (15). However, another research has demonstrated that there is no difference in serum total cholesterol or triglycerides between the NSOM and control groups (16), which is consistent with our results. HDL-C and apoA1 were positive results for NSOM in this study. As HDL-C, LDL-C, and triglyceride have interaction relations, we put these three in a group for further MVMR analysis. ApoA1 is a major protein component of HDL (24), and apoB is a major protein component of LDL (25), and we put them in another group for MVMR. According to the MVMR analysis, the causal relationship between HDL-C and apoA1 on NSOM remained significant even after adjusting for the influence of other potential confounding factors on NSOM. We did not perform the MVMR analysis for obesity factors due to



exposure	outcome	method	nsnp	pval	OR(95%CI)	CochranQ_test_P	Egger_intercept_P
Adiponectin	NSOM	MR Egger	14	0.718	0.96(0.76 - 1.21)	0.502	0.416
Adiponectin	NSOM	Weighted median	14	0.394	0.90(0.70 - 1.15)		
Adiponectin	NSOM	Inverse variance weighted	14	0.187	0.89(0.75 - 1.06)	0.526	
Adiponectin	NSOM	Simple mode	14	0.168	0.73(0.48 - 1.11)		
Adiponectin	NSOM	Weighted mode	14	0.431	1.10(0.88 - 1.38)		
Resistin	NSOM	MR Egger	13	0.394	1.14(0.85 - 1.52)	0.845	0.796
Resistin	NSOM	Weighted median	13	0.218	1.14(0.92 - 1.41)		
Resistin	NSOM	Inverse variance weighted	13	**0.045**	1.18(1.00 - 1.38)	0.89	
Resistin	NSOM	Simple mode	13	0.522	1.10(0.83 - 1.47)		
Resistin	NSOM	Weighted mode	13	0.424	1.12(0.85 - 1.47)		
leptin	NSOM	MR Egger	6	0.280	0.20(0.02 - 2.51)	0.795	0.294
leptin	NSOM	Weighted median	6	0.966	1.01(0.59 - 1.75)		
leptin	NSOM	Inverse variance weighted	6	0.730	0.93(0.62 - 1.40)	0.679	
leptin	NSOM	Simple mode	6	0.921	1.04(0.47 - 2.30)		
leptin	NSOM	Weighted mode	6	0.942	1.03(0.47 - 2.25)		
Agouti-related protein	NSOM	MR Egger	4	0.940	1.05(0.37 - 2.99)	0.023	0.872
Agouti-related protein	NSOM	Weighted median	4	0.711	1.08(0.71 - 1.63)		
Agouti-related protein	NSOM	Inverse variance weighted	4	0.607	1.14(0.70 - 1.84)	0.054	
Agouti-related protein	NSOM	Simple mode	4	0.916	1.03(0.64 - 1.66)		
Agouti-related protein	NSOM	Weighted mode	4	0.811	1.05(0.70 - 1.58)		
nerve growth factor	NSOM	MR Egger	7	0.122	0.97(0.95 - 1.00)	0.69	0.63
nerve growth factor	NSOM	Weighted median	7	**0.029**	0.97(0.95 - 1.00)		
nerve growth factor	NSOM	Inverse variance weighted	7	**0.047**	0.98(0.96 - 1.00)	0.767	
nerve growth factor	NSOM	Simple mode	7	0.304	0.97(0.93 - 1.02)		
nerve growth factor	NSOM	Weighted mode	7	0.094	0.98(0.96 - 1.00)		

FIGURE 3
Forward Mendelian randomization analysis data on adipokines and NSOM. The red text denotes the *p*-value for this trait is less than 0.05. nsnp, number of single nucleotide polymorphisms used as instrumental variables for Mendelian randomization; OR, odds ratio; CI, confidence interval; NSOM, non-suppurative otitis media.

collinearity, nor did we perform the MVMR analysis of adipokines factors due to their independence.

In the two-step MR analysis for mediation, we used both BMI and obesity as exposures. Based on the analysis results, it was known that HDL-C and apoA can be used as mediating factors between obesity and NSOM. Combined with the direction of action indicated by the OR value, obesity/BMI may downregulate the production of HDL-C/apoA, and HDL-C/apoA1 plays a protective role in the development of NSOM. Therefore, obesity promotes NSOM by downregulating HDL-C/apoA1. Although the MR Egger method did not show consistent results with the other four methods when obesity was analyzed as an exposure and apoA1 as an outcome in MR analysis, the *p*-value of the MR Egger method, which was greater than 0.05, was considered not statistically significant. In addition to the IVW method, the p-value of the weighted median method was also less than 0.05, which enhanced the reliability of the results. Although there is no direct evidence that HDL-C/apoA1 is associated with NSOM, previous studies have found that HDL-C/apoA is associated with inflammation. The low levels of HDL-C are strongly associated with, and an independent predictor of, inflammation and endothelial cell activation (26). ApoA1 can play an anti-inflammatory role by inducing M2 macrophage differentiation (27) and inhibiting neutrophil hyperactivation (28). Obesity affects HDL-C in two ways. First, it accelerates HDL-C degradation, cholesteryl ester transfer protein (CETP) and hepatic lipase activity are elevated in obese patients. Increased hepatic lipase activity promotes HDL-C catabolism to produce apoA1 and HDL-C particles, with apoA1 being recycled or degraded by the kidneys. Second, it blocks HDL-C synthesis, which is also affected by CETP. CETP inhibitors block the exchange of triglycerides and cholesterol, reduce HDL-C esterification, and improve HDL-C function (29).

Among the adipokines, resistin and NGF showed a causal relationship with NSOM. We have not found any reports about resistin or NGF related to NSOM. Resistin was a risk factor for disease, and NGF was a protective factor. The MR analysis results had *p*-values only slightly lower than 0.05 and ORs close to 1, indicating that their significance was not high. We can only consider them as factors in a potential causal relationship with NSOM. Although the sensitivity analysis of "Leave-one-out" increased the reliability of the results, further validation is still needed.

There is also a view that NSOM may lead to obesity by affecting the chorda tympani nerve, leading to changes in taste function and preference for a high-fat diet (30). In our MR analysis using NSOM as exposure and 16 factors of obesity and lipid metabolism as outcomes, no positive results were obtained, suggesting that NSOM does not directly lead to obesity and does not affect lipid metabolism.

Finally, we recommend that weight loss is a good option for NSOM patients associated with obesity, especially in children. Even for NSOM patients with normal BMI, it is necessary to avoid a high-fat diet. However, it may be a new way to treat NSOM by regulating HDL-C, apoA1, resistin, and NGF. This article reveals the relationship between obesity, lipid metabolism-related factors, and NSOM at the genetic level. Compared to observational studies, the MR analysis excluded environmental factors and clarified their causal relationships, resulting in relatively reliable results. However, this article still has certain limitations. For example, we selected GWAS datasets for adiponectin and leptin levels from a mixed population, while other GWAS datasets came from European populations, which may have potential heterogeneity. To obtain causal factors related to NSOM as much as possible to facilitate the screening of mediators, we did not correct the *p*-value of the MR analysis results, which resulted in an increased

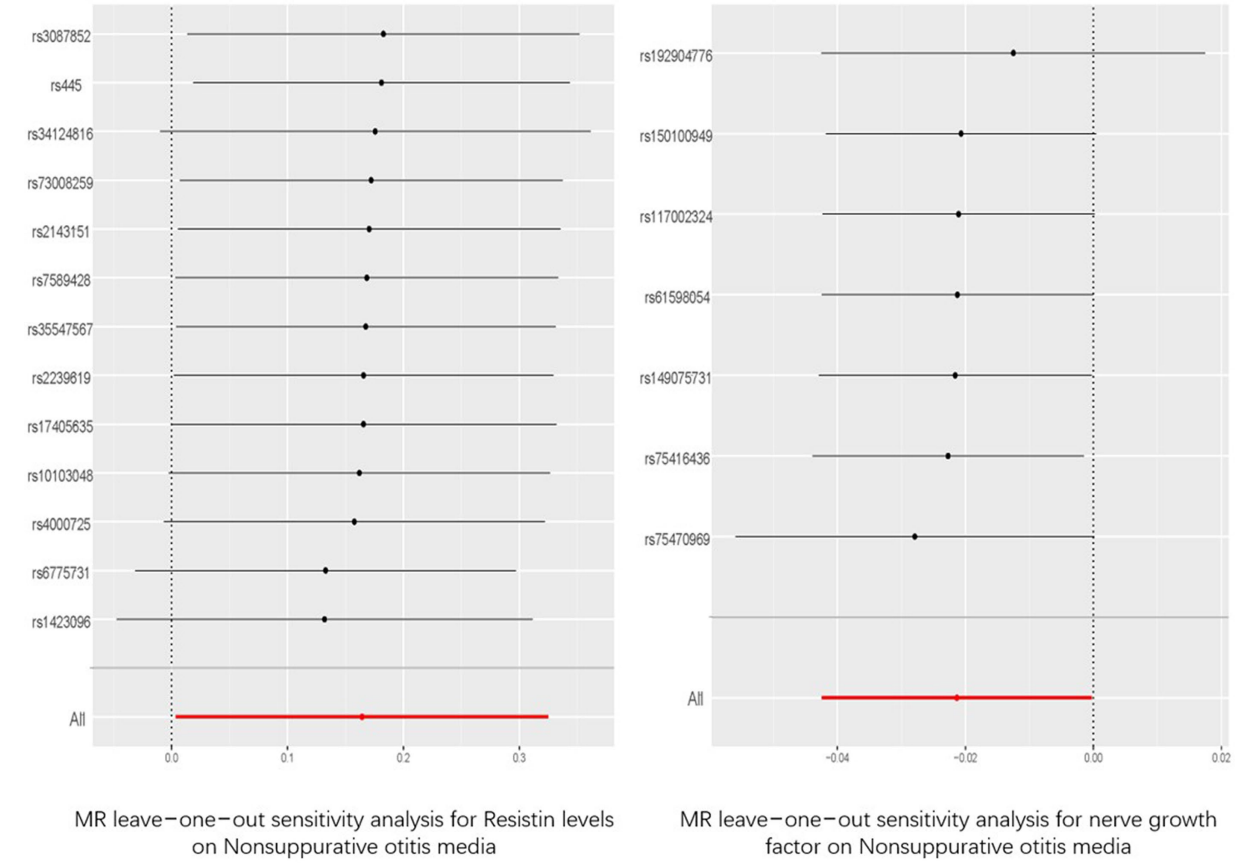


FIGURE 4
"Leave-one-out" analysis of the causal association of resisitin levels, nerve growth factor and Nonsuppurative otitis media. The 95% CI and causal estimate when each SNP was eliminated individually are shown by the black bars and dots. The fixed-effect IVW method's overall estimate and 95% confidence interval are shown by the red dot and bar. CI, confidence interval; SNP, single nucleotide polymorphism; IVW, inverse-variance weighted.

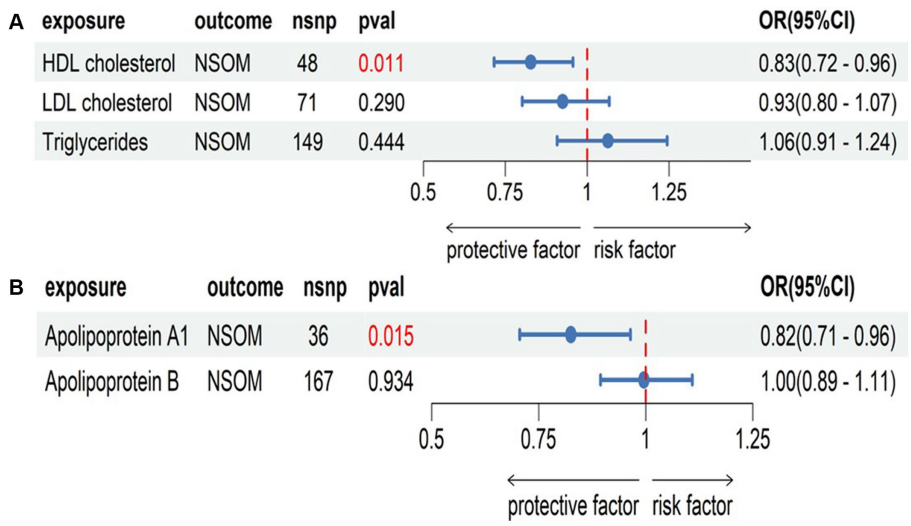


FIGURE 5
Multivariate Mendelian randomization analysis, **(A)** the group of HDL cholesterol, LDL cholesterol, and triglycerides; **(B)** the group of apolipoprotein Al and apolipoprotein B. The red text denotes that the *p*-value for this trait is less than 0.05. nsnp, the number of single nucleotide polymorphisms used as instrumental variables for NSOM, non-suppurative otitis media.

A

exposure	outcome	nsnp	method	pval	OR(95% CI)
Obesity	HDL cholesterol	5	MR Egger	0.551	0.909 (0.688 to 1.202)
		5	Weighted median	**<0.001**	0.938 (0.913 to 0.965)
		5	Inverse variance weighted	**<0.001**	0.928 (0.899 to 0.959)
		5	Simple mode	0.067	0.943 (0.900 to 0.987)
		5	Weighted mode	0.054	0.950 (0.915 to 0.986)
HDL cholesterol	NSOM	86	MR Egger	0.120	0.851 (0.696 to 1.041)
		86	Weighted median	**0.020**	0.796 (0.657 to 0.965)
		86	Inverse variance weighted	**<0.001**	0.806 (0.713 to 0.911)
		86	Simple mode	**0.013**	0.609 (0.415 to 0.893)
		86	Weighted mode	**0.015**	0.813 (0.690 to 0.957)

0.25 0.5 0.75 1 1.25

B

exposure	outcome	nsnp	method	pval	OR(95% CI)
Obesity	Apolipoprotein A1	5	MR Egger	0.409	1.139 (0.873 to 1.487)
		5	Weighted median	**0.012**	0.966 (0.941 to 0.993)
		5	Inverse variance weighted	**0.021**	0.956 (0.920 to 0.993)
		5	Simple mode	0.153	0.947 (0.891 to 1.006)
		5	Weighted mode	0.394	0.980 (0.941 to 1.021)
Apolipoprotein A1	NSOM	69	MR Egger	**0.049**	0.800 (0.644 to 0.995)
		69	Weighted median	**0.002**	0.728 (0.595 to 0.890)
		69	Inverse variance weighted	**<0.001**	0.798 (0.704 to 0.904)
		69	Simple mode	**0.013**	0.615 (0.424 to 0.894)
		69	Weighted mode	**0.004**	0.727 (0.589 to 0.897)

0.25 0.5 0.75 1 1.25

FIGURE 6
Two-step MR for mediation analysis of obesity as the exposure and NSOM as the outcome. The bold text denotes the *p*-value for this trait is less than 0.05. **(A)** The mediation is HDL cholesterol. **(B)** The mediation is apolipoprotein Al. nsnp: number of single nucleotide polymorphisms used as instrumental variables for Mendelian randomization; OR, odds ratio; CI, confidence interval; NSOM, non-suppurative otitis media.

A

exposure	outcome	nsnp	method	pval	OR(95% CI)
Body mass index	HDL cholesterol	75	MR Egger	**0.010**	0.773 (0.639 to 0.935)
		75	Weighted median	**<0.001**	0.803 (0.756 to 0.852)
		75	Inverse variance weighted	**<0.001**	0.792 (0.732 to 0.857)
		75	Simple mode	**<0.001**	0.785 (0.695 to 0.886)
		75	Weighted mode	**<0.001**	0.806 (0.753 to 0.863)
HDL cholesterol	NSOM	85	MR Egger	0.126	0.853 (0.697 to 1.044)
		85	Weighted median	**0.017**	0.797 (0.661 to 0.960)
		85	Inverse variance weighted	**<0.001**	0.807 (0.713 to 0.913)
		85	Simple mode	**0.022**	0.618 (0.412 to 0.927)
		85	Weighted mode	**0.018**	0.812 (0.686 to 0.961)

0.25 0.5 0.75 1 1.25

B

exposure	outcome	nsnp	method	pval	OR(95% CI)
Body mass index	Apolipoprotein A1	76	MR Egger	0.141	0.866 (0.716 to 1.047)
		76	Weighted median	**<0.001**	0.870 (0.816 to 0.928)
		76	Inverse variance weighted	**<0.001**	0.832 (0.769 to 0.899)
		76	Simple mode	**0.005**	0.763 (0.636 to 0.917)
		76	Weighted mode	0.071	0.920 (0.841 to 1.006)
Apolipoprotein A1	NSOM	68	MR Egger	0.052	0.802 (0.644 to 0.998)
		68	Weighted median	**0.001**	0.728 (0.602 to 0.880)
		68	Inverse variance weighted	**<0.001**	0.799 (0.705 to 0.906)
		68	Simple mode	**0.015**	0.625 (0.431 to 0.905)
		68	Weighted mode	**0.004**	0.726 (0.590 to 0.894)

0.25 0.5 0.75 1 1.25

FIGURE 7
Two-step MR for mediation analysis of body mass index as the exposure and NSOM as the outcome. The bold text denotes that the *p*-value for this trait is less than 0.05. **(A)** The mediation is HDL cholesterol. **(B)** The mediation is apolipoprotein Al. nsnp: number of single nucleotide polymorphisms used as instrumental variables for Mendelian randomization; OR, odds ratio; CI, confidence interval; NSOM, non-suppurative otitis media.

TABLE 2 The mediating effect of two-step MR mediation analysis.

Exposure	Mediator	Outcome	Beta_all	Beta1	Beta2	Beta12	Beta_dir	Beta_per
Obesity	HDL cholesterol	NSOM	0.162	−0.074	−0.216	0.016	0.146	0.099
Obesity	Apolipoprotein A1	NSOM	0.162	−0.045	−0.226	0.01	0.267	0.063
Body mass index	HDL cholesterol	NSOM	0.317	−0.233	−0.214	0.05	0.267	0.158
Body mass index	Apolipoprotein A1	NSOM	0.317	−0.184	−0.224	0.041	0.276	0.13

nsnp, number of single nucleotide polymorphisms used as instrumental variables for Mendelian randomization. NSOM, non-suppurative otitis media.

false-positive rate of the results. Second, it was not possible to group datasets and obtain information on age and gender differences; however, previous studies have mostly focused on children. Additionally, a reverse MR analysis only provided insufficient lateral evidence and did not directly validate the viewpoint in the observational study that NSOM exacerbates obesity by affecting the sense of smell. Further prospective clinical trials are needed for us to remedy these limitations and validate our results.

Conclusion

This study proposed several protective and risk factors related to obesity and lipid metabolism causality associated with NSOM. Through comprehensive analysis, we conclude that obesity and adiposity may increase the risk of developing NSOM while NSOM does not affect obesity, adiposity, or lipid metabolism. HDL-C and apoA may inhibit the progress of NSOM. In the adipokines, resistin may be a potential risk factor for NSOM, whereas NGF may be a potential protective factor. In addition, obesity may promote the development of NSOM by lowering HDL-C and apoA.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by the Ethics Committee of Shaoxing People's Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin because The datasets were obtained from the IEU Open GWAS project, which is a public database.

Author contributions

XY: Writing – original draft, Software, Investigation. SC: Writing – review & editing, Formal analysis, Data curation.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2024.1422786/full#supplementary-material

References

1. Leung AKC, Wong AHC. Acute otitis media in children. *Recent Patents Inflamm Allergy Drug Discov*. (2017) 11:32–40. doi: 10.2174/1874609810666170712145332

2. Rosenfeld RM, Shin JJ, Schwartz SR, Coggins R, Gagnon L, Hackell JM, et al. Clinical practice guideline: otitis media with effusion (update). *Otolaryngol Head Neck Surg*. (2016) 154:S1–S41. doi: 10.1177/0194599815623467

3. Masood B, Moorthy M. Causes of obesity: a review. *Clin Med*. (2023) 23:284–91. doi: 10.7861/clinmed.2023-0168

4. Drozdová D, Danková Z, Čerňanová V, Siváková D. Body composition of Slovak midlife women with cardiovascular complications. *Anthropol Rev*. (2016) 79:169–80. doi: 10.1515/anre-2016-0013

5. Dutta S, Singhal AK, Suryan V, Chandra NC. Obesity: an impact with cardiovascular and cerebrovascular diseases. *Indian J Clin Biochem*. (2023) 39:168–178. doi: 10.1007/s12291-023-01157-w

6. Klein S, Gastaldelli A, Yki-Järvinen H, Scherer PE. Why does obesity cause diabetes? *Cell Metab*. (2022) 34:11–20. doi: 10.1016/j.cmet.2021.12.012

7. Kuvat N, Tanriverdi H, Armutcu F. The relationship between obstructive sleep apnea syndrome and obesity: a new perspective on the pathogenesis in terms of organ crosstalk. *Clin Respir J*. (2020) 14:595–604. doi: 10.1111/crj.13175

8. Vorobeľová L, Falbová D, Siváková D. Differences in body composition between metabolically healthy and unhealthy midlife women with respect to obesity status. *Anthropol Rev*. (2021) 84:59–71. doi: 10.2478/anre-2021-0008

9. Alaraifi AK, Alosfoor MA, Alsaab F. Impact of pediatric obesity on the prevalence and outcome of otitis media with effusion. *Int J Pediatr Otorhinolaryngol*. (2020) 133:110005. doi: 10.1016/j.ijporl.2020.110005

10. Haksever M, Durgut O, Demirci H, Gençay S, Özmen S. Relationship between otitis media with effusions and pediatric obesity. *Int J Pediatr Otorhinolaryngol*. (2022) 161:111272. doi: 10.1016/j.ijporl.2022.111272

11. Choi HG, Sim S, Kim SY, Lee HJ. A high-fat diet is associated with otitis media with effusion. *Int J Pediatr Otorhinolaryngol*. (2015) 79:2327–31. doi: 10.1016/j.ijporl.2015.10.037

12. Lawlor DA, Harbord RM, Sterne JAC, Timpson N, Davey Smith G. Mendelian randomization: using genes as instruments for making causal inferences in epidemiology. *Stat Med*. (2008) 27:1133–63. doi: 10.1002/sim.3034

13. Cao J, Liu W, Yang Z, Qu G, Zhong C. Causal relationship between body mass index and risk of otitis media with effusion in children: a Mendelian randomization study. *Indian J Otolaryngol Head Neck Surg*. (2023) 76:1410–8. doi: 10.1007/s12070-023-04161-x

14. Hartwig FP, Davey Smith G, Bowden J. Robust inference in summary data Mendelian randomization via the zero modal pleiotropy assumption. *Int J Epidemiol*. (2017) 46:1985–98. doi: 10.1093/ije/dyx102

15. Kim JB, Park DC, Cha CI, Yeo SG. Relationship between pediatric obesity and otitis media with effusion. *Arch Otolaryngol*. (2007) 133:379–82. doi: 10.1001/archotol.133.4.379

16. Kim SH, Park DC, Byun JY, Park MS, Cha CI, Yeo SG. The relationship between overweight and otitis media with effusion in children. *Int J Obes*. (2011) 35:279–82. doi: 10.1038/ijo.2010.144

17. Kaya S, Selimoğlu E, Cureoğlu S, Selimoğlu MA. Relationship between chronic otitis media with effusion and overweight or obesity in children. *J Laryngol Otol*. (2017) 131:866–70. doi: 10.1017/S002221511700161X

18. Aoki H, Sando I, Takahashi H. Anatomic relationships between Ostmann's fatty tissue and eustachian tube. *Ann Otol Rhinol Laryngol*. (1994) 103:211–4. doi: 10.1177/000348949410300308

19. Valipour A, Makker HK, Hardy R, Emegbo S, Toma T, Spiro SG. Symptomatic gastroesophageal reflux in subjects with a breathing sleep disorder. *Chest*. (2002) 121:1748–53. doi: 10.1378/chest.121.6.1748

20. Atkinson H, Wallis S, Coatesworth AP. Otitis media with effusion. *Postgrad Med*. (2015) 127:381–5. doi: 10.1080/00325481.2015.1028317

21. Daniels SR, Khoury PR, Morrison JA. The utility of body mass index as a measure of body fatness in children and adolescents: differences by race and gender. *Pediatrics*. (1997) 99:804–7. doi: 10.1542/peds.99.6.804

22. Nevill AM, Metsios GS. The need to redefine age-and gender-specific overweight and obese body mass index cutoff points. *Nutr Diabetes*. (2015) 5:e186–6. doi: 10.1038/nutd.2015.36

23. Løkling HL, Roelants M, Kommedal KG, Skjåkødegård H, Apalset EM, Benestad B, et al. Monitoring children and adolescents with severe obesity: body mass index (BMI), BMI z-score or percentage above the International Obesity Task Force overweight cut-off?[J]. *Acta Paediatrica*. (2019) 108:2261–6.

24. Hafiane A, Gianopoulos I, Sorci-Thomas MG, Daskalopoulou SS. Current models of apolipoprotein AI lipidation by adenosine triphosphate binding cassette transporter A1. *Curr Opin Lipidol*. (2022) 33:139–45. doi: 10.1097/MOL.0000000000000786

25. Parhofer KG, Daugherty A, Kinoshita M, Schonfeld G. Enhanced clearance from plasma of low density lipoproteins containing a truncated apolipoprotein, apoB-89. *J Lipid Res*. (1990) 31:2001–7. doi: 10.1016/S0022-2275(20)42264-3

26. Wan Ahmad WNH, Sakri F, Mokhsin A, Rahman T, Mohd Nasir N, Abdul-Razak S, et al. Low serum high density lipoprotein cholesterol concentration is an independent predictor for enhanced inflammation and endothelial activation. *PLoS One*. (2015) 10:e0116867. doi: 10.1371/journal.pone.0116867

27. Datta G, Kramer PA, Johnson MS, Sawada H, Smythies LE, Crossman DK, et al. Bioenergetic programming of macrophages by the apolipoprotein AI mimetic peptide 4F. *Biochem J*. (2015) 467:517–27. doi: 10.1042/BJ20131635

28. Blackburn WD, Dohlman JG, Venkatachalapathi YV, Pillion DJ, Koopman WJ, Segrest JP, et al. Apolipoprotein AI decreases neutrophil degranulation and superoxide production. *J Lipid Res*. (1991) 32:1911–8. doi: 10.1016/S0022-2275(20)41894-2

29. Brown ML, Inazu A, Hesler CB, Agellon LB, Mann C, Whitlock ME, et al. Molecular basis of lipid transfer protein deficiency in a family with increased high-density lipoproteins. *Nature*. (1989) 342:448–51. doi: 10.1038/342448a0

30. Shin IH, Park DC, Kwon C, Yeo SG. Changes in taste function related to obesity and chronic otitis media with effusion. *Archives Otolaryngol*. (2011) 137:242–6. doi: 10.1001/archoto.2011.23

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Measuring calf circumference in frail hospitalized older adults and prediction of in-hospital complications and post-discharge mortality

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Background: Sarcopenia, characterized by muscle mass, strength, and performance decline, significantly impacts outcomes in older adults. This study aims to assess the predictive value of calf circumference (CC), in conjunction with SARC-F and hand grip, concerning in-hospital complications and post-discharge mortality among hospitalized frail older adults.

Methods: A cohort of 158 hospitalized patients aged over 65 years underwent Comprehensive Geriatric Assessment and sarcopenia screening, including CC measurement. Multivariable regression analyses, adjusted for confounders, were conducted to assess predictive associations.

Results: The study cohort, comprising 53% males with a median age of 86 years, exhibited significant sarcopenia prevalence based on SARC-F (85% indicating sarcopenia), hand grip strength (probable sarcopenia in 77% of males and 72% of females), and CC (sarcopenia in 83%). Multivariate analysis, adjusting for age, sex, Clinical Frailty Scale (CFS), and Mini Nutritional Assessment-Short Form (MNA-SF), demonstrated associations of CC and SARC-F with in-hospital complications, while CC also showed a significant association with reduced risks of in-hospital mortality (OR 0.441, 95% CI 0.257 to 0.754, $p = 0.003$) and 90-day mortality (OR 0.714, 95% CI 0.516 to 0.988, $p = 0.043$).

Conclusion: This study provides insights into the predictive accuracy of sarcopenia screening tools on mortality in real-world hospitalized older adults with frailty. Notably, CC emerges as a robust predictor of mortality outcomes. Further research is warranted to validate and elucidate the respective contributions of CC and frailty to mortality in vulnerable populations.

KEYWORDS

calf circumference, sarcopenia, frailty, mortality, in-hospital complications

Introduction

Sarcopenia is a progressive and generalized skeletal muscle disorder characterized by reduced muscle mass, strength, and performance, associated with an increased likelihood of experiencing adverse outcomes including falls, fractures, physical disability, and mortality (1, 2).

Its prevalence ranges from 7.5% in community-dwelling older adults to 77.6% in patients undergoing rehabilitation or post-acute care (3). Up to 15% of hospitalized older adults may develop sarcopenia at discharge (4). Sarcopenia is secondary to reduced physical activity (bed rest, and physical deconditioning), multimorbidity, nutritional factors (malnutrition with or without malabsorption, gastroenteric diseases), and polypharmacy. Notably, sarcopenia is also strongly associated with frailty, a geriatric syndrome characterized by an extreme vulnerability to endogenous and exogenous stressors, resulting from age-related depletion of the body's homeostatic reserves (5). Frailty and sarcopenia share commonalities such as muscle atrophy, dynapenia, and impaired physical function; malnutrition may be considered a harbinger between the two, ultimately leading to an acceleration of the frailty trajectory (6).

In 2019 a revised diagnostic algorithm for sarcopenia (2nd edition of the European Working Group on Sarcopenia in Older People, EWGSOP2) (7) was proposed and the SARC-F questionnaire was recommended for screening (8). SARC-F is a questionnaire consisting of five questions concerning Strength (S), Assistance with walking (A), Rising from a chair (R), Climbing stairs (C), and Falls (F). Growing evidence has underscored the role of sarcopenia screening in predicting in-hospital immediate mortality in older adults. Namely, in a Japanese retrospective study conducted on over 2.400 hospitalized over-65 patients, SARC-F score was associated with increased in-hospital mortality within 30 days (9). Similarly, a recent meta-analysis found a significant association between SARC-F and long-term mortality (<5 years) in very old age patients (10). However, Volker et al., observed high heterogeneity in the clinometric properties of SARC-F, with a wider range of sensitivity (29–55%) and specificity (69–89%) in different settings, suggesting that the addition of calf circumference (CC) could improve sensitivity, especially in community-dwellings (11). Indeed, combining calf and thigh circumferences with SARC-F is reported to enhance the diagnostic accuracy for sarcopenia in individuals aged 60 and above, providing a resource-efficient diagnostic tool (2).

CC nowadays is included in all major international consensus (7, 12, 13) and it is considered a reliable screening tool for sarcopenia and a promising prognostic indicator in older adults. Indeed, calf measurements are associated with higher readmissions and mortality rates in hospitalized older adults (14–17). In addition, measurement of the stability of CC over 4 years was associated with decreased mortality risk in a cohort of 904 community-dwelling older adults (mean age 83.8 ± 12.2) (18). Moreover, Wu and Chen demonstrated that the addition of CC to traditional measures of sarcopenia (hand grip strength, speed of gait, muscle mass) correlated with higher all-cause and CV mortality risks after a follow-up of 3 years in community-dwelling people aged 50 years or more (19).

In Japan, Ishii et al. developed a formula based on age, CC, and hand grip strength that predicts the probability of developing sarcopenia (20), which also demonstrated high sensitivity and specificity when diagnosing sarcopenia in community-dwelling adults and inpatients (21–23) or predicting long-term all-cause mortality in hospitalized older adults (24, 25).

Based on this background, the present study aims to assess the predictive accuracy of three sarcopenia evaluation tools (SARC-F, CC, and hand grip) on intra-hospital complication rate, in-hospital mortality, and mortality within 90 days post-hospital discharge in a cohort of hospitalized older adults.

Method

This is a prospective observational study conducted on hospitalized older adults (aged over 65 years old) referred to two units (Geriatric Clinic and Transitional Care Unit) of IRCCS Hospital Polyclinic San Martino in Genoa, Italy, from January to May 2023. Patients admitted to the Geriatric Clinic ward came from the Emergency Room, while those admitted to the Transitional Care ward came from other wards of the Polyclinic and were awaiting discharge to nursing homes.

Inclusion criteria were: age 65 or older, acceptance of informed consent by the patient or patient's legal representative. Exclusion criteria included: age under 65, lack of acceptance or withdrawal of informed consent, and patients diagnosed with end-stage diseases in need of palliative care (eg. dementia CDR 5, heart failure NYHA IV, COPD with acute respiratory failure).

Upon admission, demographic data were collected. All patients received a Comprehensive Geriatric Assessment (CGA) (26) within 72 h from admission, including Clinical Frailty Scale (CFS) (27) to assess frailty status; number of medications and ABC score to assess polypharmacy and anticholinergic burden; basic and instrumental activities of daily living (ADL and IADL) (28) to assess functional status; Short Portable Mental Status Questionnaire (SPMSQ) (29) to evaluate cognitive performance; Cumulative Illness Rating Scale (CIRS) (30) to assess multimorbidity, and Clinical Dementia Rating Scale (CDR) (31) to stratify the severity of dementia. We used the Mini Nutritional Assessment – Short Form (MNA-SF) (32) to screen for malnutrition. SARC-F (33), measurement of CC, and hand grip (HG, using a GIMA 28791 Smedley dynamometer) were used to evaluate sarcopenia. The standardized Asian Working Group for Sarcopenia (AWGS19) protocol (12) was adopted for evaluating CC, measuring the maximum value of both calves using a non-elastic tape, applying AWGS19 cut-offs: males <34 cm; females <33 cm. As for HG, we employed cut-offs from EWGSOP2 (7): males <27 kg, females <16 kg.

Hospital complication rate was documented, including incident delirium (defined as a score of 4 or higher on the 4AT test) (34), pressure ulcers, acute anemia (hemoglobin <9 g/dL), hospital-acquired infections, sepsis, catheterization during hospital stay, urinary tract infections, respiratory distress, acute heart failure, immobilization syndrome, and in-hospital mortality. In-hospital stay and discharge destination were also collected. 90-day mortality rate after post-hospital discharge was recorded through the ASL3 Genoa (Italy) county electronic database. A Complication Index was derived as the pooled rate of incidence of any of the examined complications.

The protocol was approved by the IRB (CERA N 2024-54 12/06/2024, University of Genoa, Italy) and met the guidelines of the local Governmental Agency. Patients or their proxies provided written

informed consent before study inclusion. The study was performed in adherence to the Declaration of Helsinki.

Statistical analysis

Descriptive data were reported as mean with standard deviation or median with IQR. Multivariable logistic regression was used to assess the association between sarcopenia screening tests and clinical variables. Logistic regression for dichotomic outcomes (in-hospital mortality and 90-day mortality), and linear regression for continuous outcomes (Complication Index) were used. Multivariate regression models were built using the three sarcopenia assessment methods (SARCF, CC, hand grip) and adjusted for possible confounders: sex, age, nutritional status (MNA-SF), and frailty status (CFS). An advanced statistical imputation method was applied to avoid biases from the absence of data in hand grip measurement. All reported analyses were run by RStudio (Version 2022.07) and a two-sided α less than 0.05 was considered statistically significant.

TABLE 1 Clinical phenotype of the population.

	Total ($N = 158$)
Sex (n[%])	
Male	83 (53%)
Female	75 (47%)
Age (median[IQR])	86 (9)
Origin	
Home	141 (89%)
Residential care home	17 (11%)
CFS (median[IQR])	6 (2)
CIRS (median[IQR])	
Severity index	1.53 (0.41)
Comorbidity index	3 (2)
Polypharmacy (average[sd])	5.62 (3.33)
ACB score (average[sd])	1.35 (1.38)
ADL (median[IQR])	2 (4)
IADL (median[IQR])	1 (3)
SPMSQ (median[IQR])	5 (7)
CDR (median[IQR])	1 (2)
MNA-SF (median[IQR])	8 (5)
At risk (8–11 ppt)	87 (55%)
Malnourished (≤7 ppt)	59 (37%)
SARC-F (median[IQR])	5 (4)
≥4 ppt	135 (85%)
Hand grip (median[IQR])	14 (9)
Male* (<27 kg)	64 (77%)
Female* (<16 kg)	54 (72%)
Calf circumference (median[IQR])	29.5 (5)
Male** (<34 cm)	69 (83%)
Female** (<33 cm)	62 (83%)

CFS: clinical frailty scale; MNA-SF: mini nutritional assessment-short form; CC: calf circumference; HG: hand grip; IQR: interquartile range; sd: standard deviation. *EWGSOP2 criteria; **AWGS 19 criteria.

Results

158 consecutive patients (53% male) were enrolled. As shown in Table 1, age ranged from 65 years to 101 years, with a median of 86 years (IQR 9). Upon admission, the clinical phenotype of patients was frail (median CFS 6, IQR 2) with functional decline (median ADL 2, IQR 4; median IADL 1, IQR 3), and 61% had a diagnosis of dementia (CDR >1). The most frequent complications were hospital-acquired infections (90 cases, 57%), delirium (89 cases, 56%), occurrence of pressure ulcers (51 cases, 32%); immobilization syndrome occurred in more than one third of the cases (33 patients, 34%).

Regarding nutritional assessment, MNA-SF median score was 8 (IQR 5), indicating that the majority of the population was at risk of malnutrition; only 8% of the population had a normal nutritional status. As for sarcopenia screening, SARC-F median score was 5 (IQR 4); most of the analyzed subjects (85%) were suggestive of sarcopenia. At the HG test, the median value was 14 kg (IQR 9); according to EWGSOP2 criteria, 77% of male subjects and 72% of female subjects were found to have probable sarcopenia. Measuring CC, the mean value was 29.5 cm (IQR 5), meaning that sarcopenia was present in 83% of patients according to AWGS19 criteria.

By matching the data of HG and CC, a diagnosis of sarcopenia was made in 63% of our population ($n = 99$); stratifying by sex, sarcopenia was found in 66% of males ($n = 55$) and 59% of females ($n = 44$).

Hand grip strength could not be assessed in 26 out of 158 patients (including 12 men and 14 women). The multivariate statistical analysis (Table 2), adjusted for possible confounding variables showed that CC (β −0.329, 95% CI -0.477 to −0.182, p-value <0.001) and MNA-SF (β −0.380, 95% CI -0.564 to −0.196, p-value <0.001) were associated with the in-hospital complication rate. This result was confirmed in a sub-analysis showing that CC was the major clinical variable associated with all major in-hospital complications (see Supplementary materials); in particular, the lower the CC, the higher the risk of developing in-hospital complications and dying during hospitalization or within 90 days of discharge.

On the other hand, SARC-F (OR 2.268, 95% CI 1.191–4.317, p-value 0.013) and CC (OR 0.440, 95% CI 0.257 to 0.754, p-value 0.003) were associated with in-hospital mortality. Eventually, CC was associated with 90-day mortality (OR 0.714, 95% CI 0.516 to 0.988, p-value 0.043). Adding CIRS as an additional covariate to the multivariate model did not significantly impact the results.

Discussion

The alarming prevalence of sarcopenia in hospitalized older adults with multimorbidity and frailty, and its association with adverse clinical outcomes, underscores the need for systematic routine screenings to overcome underdiagnosis and undertreatment. So far, there is a lack of standardization and implementation of hospital screening for sarcopenia, and a paucity of studies have investigated the association between screening tools and clinical outcomes in

TABLE 2 Multivariate models adjusted for sex, age and frailty status.

	In-hospital mortality		Complication Index		90-day mortality	
	OR (95%CI)	*p*	β (95%CI)	*p*	OR (95%CI)	*p*
Age	1.083 (0.978–1.199)	0.127	−0.001 (−0.047–0.044)	0.959	1.064 (0.970–1.166)	0.186
Sex	10.692 (0.800–142.939)	0.073	0.322 (−0.630–1.273)	0.504	1.111 (0.118–10.439)	0.926
CFS	0.511 (0.164–1.593)	0.247	−0.028 (−0.425–0.368)	0.888	1.266 (0.526–3.045)	0.598
MNA-SF	0.657 (0.396–1.092)	0.105	−0.380 (−0.564- -0.196)	**<0.001**	1.131 (0.782–1.635)	0.514
SARC-F	2.268 (1.192–4.317)	**0.013**	0.133 (−0.059–0.325)	0.174	1.500 (0.983–2.288)	0.060
CC	0.441 (0.257–0.755)	**0.003**	−0.330 (−0.477- -0.182)	**<0.001**	0.714 (0.516–0.989)	**0.043**
HG	1.288 (0.922–1.798)	0.135	0.037 (−0.067–0.140)	0.482	1.147 (0.876–1.501)	0.313

CFS: clinical frailty scale; MNA-SF: mini nutritional assessment-short form; CC: calf circumference; HG: hand grip.
Bold values mean statistically significant results ($p < 0.05$).

hospitalized older patients, with a wide heterogeneity in study designs and clinical findings (35).

To the best of our knowledge, this is the first study to assess the predictive accuracy of a series of screening tools for sarcopenia on mortality in a real-world hospitalized old population with frailty. Notably, in our hands, CC was the main determinant of 90-day mortality, while also being associated with the in-hospital complication rate and intra-hospital mortality. Similarly, also a higher SARC-F score was associated with intra-hospital mortality and a higher MNA-SF score with the in-hospital complication rate.

In line with that, Marchasson et al. showed that CC is an independent prognostic score for 1-year mortality in oncogeriatric patients submitted to chemotherapy (36). Rodrigues et al. demonstrated that CC was an accurate predictor for 36-month mortality in a cohort of 173 patients older than 60 years, undergoing maintenance hemodialysis (37). Moreover, Aliberti et al. evaluated 1-year survival of 665 acutely ill older adults and CC was the main determinant for mortality after adjustment for age, sex, race, income, Charlson comorbidity index, depressive symptoms, cognitive impairment, and unintentional weight loss (38). Recently, Li et al. observed that a 1 cm increase in CC is associated with a decrease in overall mortality in different healthcare settings (39). The recent systematic review and meta-analysis by Wei et al. confirmed the association between low CC and mortality in hospitalized adults (pooled HR = 2.63, 95% CI 1.93–3.58) (15).

A major strength of our findings is the systematic assessment of frailty and its incorporation as a covariate. Although frailty is recognized as a critical factor in predicting adverse outcomes in older adults, including mortality, CFS was not predictive of mortality. This contrasts with the study of Liao et al. (40), which showed that mortality in older adults visiting the emergency room was associated with gender, possible sarcopenia (defined by both low handgrip strength and CC), living in residential institutions and frailty based on Fried's phenotype (41). On one hand, our study focused on advanced age groups, and the incorporation of frailty based on an accumulation model (42), although in the screening format, may have a higher likelihood to capture a broader range of frailty-related variables and their interaction with CC (43). On the other hand, the inability of the CFS to predict mortality may also be due to a 'ceiling effect,' as the great majority of patients had an advanced frailty status that may limit the generalization of the findings.

Furthermore, our study design is marked by the inclusion of a 90-day follow-up period, representing a clinical advancement over short-term mortality assessment (44).

Additionally, by adjusting our results for MNA-SF data, we aimed to account for the potential influence of nutritional status on the association between CC and mortality outcomes. This allows us to better understand the independent prognostic value of CC in our study population.

A relevant future development would be implementing adjustment for BMI, as suggested by Gonzalez et al. (45), or, otherwise, the adoption of normative values of CC across ages. In line with that, Martone et al. (46), through the Lookup 7+ project, showed that calf circumference decreases with advancing age in both sex. Based on these findings, a simple and practical medical device—a calf circumference measuring tape—has been developed, enabling a quick and cost-effective assessment of muscle mass. Integrating normative values for calf circumference across age groups holds promise for enhancing sarcopenia assessment and for providing a better understanding of age-related variations in muscle mass, in order to identify individuals at risk of adverse outcomes.

While CC has significant evidence as a practical tool for providing an estimate of muscle mass, there's a gap in defining cut-off points. We used the AWGS19 threshold, higher than EWGSOP2 (31 cm), supported by Fernandes et al., who found mortality risk rising below 34.5 cm in people aged over 60.

The study has limitations, such as the limited sample size, the single hospital enrollment, and the possible inclusion of patients with specific conditions affecting CC (e.g., heart disease, venous insufficiency, or declivous edema). While patients admitted to the Transitional Care ward suffered from the most diverse diagnoses, those coming to the Geriatric Clinic ward directly from the Emergency Room usually had a chronic disease exacerbation (e.g., COPD, heart failure) or complications related to advanced frailty (ab ingestis pneumonia, pressure ulcers infections, urosepsis), and we did not systematically collect the causes for hospitalization. Hand grip strength assessment faced challenges, with some data missing due to poor compliance, altered consciousness, and cognitive impairment in certain patients. The presence of several missing data within the hand grip variable is undoubtedly a significant limitation of the study; excluded patients are highly likely to overlap with those most affected by sarcopenia, potentially leading to biased results and limiting the ability to accurately assess

the relationship between hand grip strength and sarcopenia. Even among those tested, conditions like bed rest and acute illness may underestimate prehensile strength on admission. It cannot be ruled out that these factors contributed to the worse predictive performance of the hand grip test, which still remains the international gold standard for the assessment of sarcopenia.

CC could indeed represent a parameter as simple and time-saving as versatile in the hospital setting, where the performance of articulated test batteries or complex physical performance tests is prevented by the often precarious and acute condition of patients. Its easy reproducibility, even by caregivers, and, at the same time, prognostic efficacy for both short- and long-term health outcomes, makes it an useful indicator for the correct assessment of geriatric patients in multiple settings, transcending the simple evaluation of sarcopenia or nutritional status.

In conclusion, based on our findings, CC emerges as a single variable capable of being associated with three important health outcomes, bearing independent prognostic value compared to nutritional and physical performance data. Due to its ease of use, we anticipate its increasing integration into routine assessments. Its predictive value for mortality outcomes in hospitalized older adults potentially surpasses frailty in this regard. However, further research is needed to confirm and better understand the relative contributions of CC and frailty to mortality in such vulnerable populations.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by University Research Ethics Committee (CERA, UniGE). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

SC: Writing – original draft, Data curation, Conceptualization. SO: Writing – review & editing, Writing – original draft. LT: Writing – review & editing, Methodology, Formal analysis. AC: Writing – review & editing, Supervision. AS: Writing – review & editing, Methodology, Formal analysis. MP: Writing – review & editing, Formal analysis. CM: Writing – review & editing, Formal analysis. AN: Writing – review & editing, Supervision. FM: Writing – review & editing, Supervision, Conceptualization.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

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References

1. Volkert D, Beck AM, Cederholm T, Cruz-Jentoft A, Hooper L, Kiesswetter E, et al. ESPEN practical guideline: clinical nutrition and hydration in geriatrics. *Clin Nutr*. (2022) 41:958–89. doi: 10.1016/j.clnu.2022.01.024

2. Mienche M, Setiati S, Setyohadi B, Kurniawan J, Laksmi PW, Ariane A, et al. Diagnostic performance of calf circumference, thigh circumference, and SARC-F questionnaire to identify sarcopenia in elderly compared to Asian working Group for Sarcopenia's diagnostic standard. *Acta Medica Indones*. (2019) 51:117–27.

3. Daly RM, Iuliano S, Fyfe JJ, Scott D, Kirk B, Thompson MQ, et al. Screening, diagnosis and Management of Sarcopenia and Frailty in hospitalized older adults: recommendations from the Australian and new Zealand Society for Sarcopenia and Frailty Research (ANZSSFR) expert working group. *J Nutr Health Aging*. (2022) 26:637–51. doi: 10.1007/s12603-022-1801-0

4. Martone AM, Bianchi L, Abete P, Bellelli G, Bo M, Cherubini A, et al. The incidence of sarcopenia among hospitalized older patients: results from the glisten study. *J Cachexia Sarcopenia Muscle*. (2017) 8:907–14. doi: 10.1002/jcsm.12224

5. Morley JE, Vellas B, Abellan van Kan G, Anker SD, Bauer JM, Bernabei R, et al. Frailty consensus: a call to action. *J Am Med Dir Assoc*. (2013) 14:392–7. doi: 10.1016/j.jamda.2013.03.022

6. Cruz-Jentoft AJ, Kiesswetter E, Drey M, Sieber CC. Nutrition, frailty, and sarcopenia. *Aging Clin Exp Res*. (2017) 29:43–8. doi: 10.1007/s40520-016-0709-0

7. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, et al. Sarcopenia: revised European consensus on definition and diagnosis. *Age Ageing*. (2019) 48:601. doi: 10.1093/ageing/afz046

8. Malmstrom TK, Miller DK, Simonsick EM, Ferrucci L, Morley JE. SARC-F: a symptom score to predict persons with sarcopenia at risk for poor functional outcomes. *J Cachexia Sarcopenia Muscle*. (2016) 7:28–36. doi: 10.1002/jcsm.12048

9. Ueshima J, Maeda K, Ishida Y, Shimizu A, Inoue T, Nonogaki T, et al. SARC-F predicts mortality risk of older adults during hospitalization. *J Nutr Health Aging*. (2021) 25:914–20. doi: 10.1007/s12603-021-1647-x

10. Ida S, Kaneko R, Imataka K, Okubo K, Shirakura Y, Azuma K, et al. Verification of the predictive validity for mortality of the SARC-F questionnaire based on a meta-analysis. *Aging Clin Exp Res*. (2021) 33:835–42. doi: 10.1007/s40520-020-01585-1

11. Voelker SN, Michalopoulos N, Maier AB, Reijnierse EM. Reliability and concurrent validity of the SARC-F and its modified versions: a systematic review and Meta-analysis. *J Am Med Dir Assoc*. (2021) 22:1864–1876.e16. doi: 10.1016/j.jamda.2021.05.011

12. Chen L-K, Woo J, Assantachai P, Auyeung TW, Chou MY, Iijima K, et al. Asian working Group for Sarcopenia: 2019 consensus update on sarcopenia diagnosis and treatment. *J Am Med Dir Assoc*. (2020) 21:300–307.e2. doi: 10.1016/j.jamda.2019.12.012

13. Studenski SA, Peters KW, Alley DE, Cawthon PM, McLean RR, Harris TB, et al. The FNIH sarcopenia project: rationale, study description, conference recommendations, and final estimates. *J Gerontol A Biol Sci Med Sci*. (2014) 69:547–58. doi: 10.1093/gerona/glu010

14. Rose Berlin Piodena-Aportadera M, Lau S, Chew J, Lim JP, Ismail NH, Ding YY, et al. Calf circumference measurement protocols for sarcopenia screening: differences in agreement, convergent validity and diagnostic performance. *Ann Geriatr Med Res*. (2022) 26:215–24. doi: 10.4235/agmr.22.0057

15. Wei J, Jiao J, Chen CL, Tao WY, Ying YJ, Zhang WW, et al. The association between low calf circumference and mortality: a systematic review and meta-analysis. *Eur Geriatr Med*. (2022) 13:597–609. doi: 10.1007/s41999-021-00603-3

16. Leandro-Merhi VA, de Aquino JLB, Reis LO. Predictors of nutritional risk according to NRS-2002 and calf circumference in hospitalized older adults with neoplasms. *Nutr Cancer*. (2017) 69:1219–26. doi: 10.1080/01635581.2017.1367942

17. Real GG, Frühauf IR, Sedrez JHK, Dall'Aqua EJF, Gonzalez MC. Calf circumference: a marker of muscle mass as a predictor of hospital readmission. *J Parenter Enter Nutr*. (2018) 42:1272–9. doi: 10.1002/jpen.1170

18. Wang X, Ying Y, Pei M, Ma X, Sun Y, Wang Y, et al. Calf circumference change and all-cause mortality among community-dwelling Chinese older people. *Clin Nutr*. (2023) 42:277–81. doi: 10.1016/j.clnu.2023.01.002

19. Wu SE, Chen WL. Calf circumference refines sarcopenia in correlating with mortality risk. *Age Ageing*. (2022) 51:afab239. doi: 10.1093/ageing/afab239

20. Ishii S, Tanaka T, Shibasaki K, Ouchi Y, Kikutani T, Higashiguchi T, et al. Development of a simple screening test for sarcopenia in older adults. *Geriatr Gerontol Int*. (2014) 14:93–101. doi: 10.1111/ggi.12197

21. Li M, Kong Y, Chen H, Chu A, Song G, Cui Y. Accuracy and prognostic ability of the SARC-F questionnaire and Ishii's score in the screening of sarcopenia in geriatric inpatients. *Braz J Med Biol Res*. (2019) 52:e8204. doi: 10.1590/1414-431x20198204

22. Erdogan T, Catikkas NM, Oren MM, Kılıc C, Karan MA, Bahat G. Ishii test for screening sarcopenia: performance in community-dwelling older adults. *Aging Clin Exp Res*. (2022) 34:785–91. doi: 10.1007/s40520-021-01998-6

23. Alsadany MA, Sanad HT, Elbanouby MH, Ali S. Detecting a valid screening method for sarcopenia in acute care setting. *J Frailty Sarcopenia Falls*. (2021) 6:111–8. doi: 10.22540/JFSF-06-111

24. Tang T, Wu L, Yang L, Jiang J, Hao Q, Dong B, et al. A sarcopenia screening test predicts mortality in hospitalized older adults. *Sci Rep*. (2018) 8:2923. doi: 10.1038/s41598-018-21237-9

25. Cavalheiro A, Afonso S, Silva M, Ramalhão N, Machado J, Magalhães S. Evaluation of probable Sarcopenia's prevalence in hospitalized geriatric patients using Ishii's score. *Cureus*. (2023) 15:e49158. doi: 10.7759/cureus.49158

26. Parker SG, McCue P, Phelps K, McCleod A, Arora S, Nockels K, et al. What is comprehensive geriatric assessment (CGA)? An umbrella review. *Age Ageing*. (2018) 47:149–55. doi: 10.1093/ageing/afx166

27. Rockwood K. A global clinical measure of fitness and frailty in elderly people. *Can Med Assoc J*. (2005) 173:489–95. doi: 10.1503/cmaj.050051

28. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. *The Gerontologist*. (1969) 9:179–86. doi: 10.1093/geront/9.3_Part_1.179

29. Pfeiffer E. A short portable mental status questionnaire for the assessment of organic brain deficit in elderly patients†. *J Am Geriatr Soc*. (1975) 23:433–41. doi: 10.1111/j.1532-5415.1975.tb00927.x

30. Conwell Y, Forbes NT, Cox C, Caine ED. Validation of a measure of physical illness burden at autopsy: the cumulative illness rating scale. *J Am Geriatr Soc*. (1993) 41:38–41. doi: 10.1111/j.1532-5415.1993.tb05945.x

31. Morris JC. The clinical dementia rating (CDR): current version and scoring rules. *Neurology*. (1993) 43:2412. doi: 10.1212/WNL.43.11.2412-a

32. Liu H, Jiao J, Zhu M, Wen X, Jin J, Wang H, et al. Nutritional status according to the short-form Mini nutritional assessment (MNA-SF) and clinical characteristics as predictors of length of stay, mortality, and readmissions among older inpatients in China: a National Study. *Front Nutr*. (2022) 9:815578. doi: 10.3389/fnut.2022.815578

33. Perna S, Gasparri C, Ferraris C, Barrile GC, Cavioni A, Mansueto F, et al. Validation of the Italian version of the SARC-F questionnaire to assess sarcopenia in older adults. *Nutrients*. (2022) 14:2533. doi: 10.3390/nu14122533

34. Bellelli G, Morandi A, Davis DHJ, Mazzola P, Turco R, Gentile S, et al. Validation of the 4AT, a new instrument for rapid delirium screening: a study in 234 hospitalised older people. *Age Ageing*. (2014) 43:496–502. doi: 10.1093/ageing/afu021

35. Lu J-L, Ding LY, Xu Q, Zhu SQ, Xu XY, Hua HX, et al. Screening accuracy of SARC-F for sarcopenia in the elderly: a diagnostic Meta-analysis. *J Nutr Health Aging*. (2021) 25:172–82. doi: 10.1007/s12603-020-1471-8

36. Bourdel-Marchasson I, Diallo A, Bellera C, Blanc-Bisson C, Durrieu J, Germain C, et al. One-year mortality in older patients with Cancer: development and external validation of an MNA-based prognostic score. *PLoS One*. (2016) 11:e0148523. doi: 10.1371/journal.pone.0148523

37. Rodrigues J, Santin F, Brito FDSB, Lindholm B, Stenvinkel P, Avesani CM. Nutritional status of older patients on hemodialysis: which nutritional markers can best predict clinical outcomes? *Nutrition*. (2019) 65:113–9. doi: 10.1016/j.nut.2019.03.002

38. Aliberti MJR, Szlejf C, Covinsky KE, Lee SJ, Jacob-Filho W, Suemoto CK. Prognostic value of a rapid sarcopenia measure in acutely ill older adults. *Clin Nutr*. (2020) 39:2114–20. doi: 10.1016/j.clnu.2019.08.026

39. Li X, Lang X, Peng S, Ding L, Li S, Li Y, et al. Calf circumference and all-cause mortality: a systematic review and Meta-analysis based on trend estimation approaches. *J Nutr Health Aging*. (2022) 26:826–38. doi: 10.1007/s12603-022-1838-0

40. Liao M-C, Yen C-C, Lin Y-T, Huang F-D, Chang YT. Sarcopenia is associated with mortality in non-critical elderly patients visiting the emergency department. *Front Med*. (2023) 9:1027503. doi: 10.3389/fmed.2022.1027503

41. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci*. (2001) 56:M146–57. doi: 10.1093/gerona/56.3.M146

42. Searle SD, Mitnitski A, Gahbauer EA, Gill TM, Rockwood K. A standard procedure for creating a frailty index. *BMC Geriatr*. (2008) 8:24. doi: 10.1186/1471-2318-8-24

43. Xu KY, Wang JJ, Chen J, Zhao X, Yuan LF, Zhang Q. Calf circumference predicts frailty in older adults: the Chinese longitudinal healthy longevity survey. *BMC Geriatr*. (2022) 22:936. doi: 10.1186/s12877-022-03644-w

44. Fernandes DPS, Juvanhol LL, Lozano M, Ribeiro AQ. Calf circumference is an independent predictor of mortality in older adults: an approach with generalized additive models. *Nutr Clin Pract Off Publ Am Soc Parenter Enter Nutr*. (2022) 37:1190–8. doi: 10.1002/ncp.10780

45. Gonzalez MC, Mehrnezhad A, Razaviarab N, Barbosa-Silva TG, Heymsfield SB. Calf circumference: cutoff values from the NHANES 1999-2006. *Am J Clin Nutr*. (2021) 113:1679–87. doi: 10.1093/ajcn/nqab029

46. Martone AM, Ciciarello F, Galluzzo V, Calvani R, Zazzara MB, Tosato M, et al. A simple medical device development according to normative values of calf circumference across ages: results from the Italian longevity check-up 7+ (lookup 7+) project. *J Cachexia Sarcopenia Muscle*. (2023) 15:36–44. doi: 10.1002/jcsm.13286

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Unraveling the obesity paradox in small cell lung cancer immunotherapy: unveiling prognostic insights through body composition analysis

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Background: The advent of immunotherapy has changed the landscape of SCLC treatment, although the identification of reliable prognostic biomarkers remains a formidable challenge. Our objective was to investigate the prognostic implications of obesity and body composition in SCLC immunotherapy while seeking a straightforward anthropometric measure.

Methods: This retrospective study analyzed data from patients with SCLC who underwent immunotherapy between 2019 and 2023. Body composition and waist circumference (WC) were analyzed using 3D slicer software on baseline CT images. Quantitative measures, including skeletal muscle index (SMI), total adipose tissue index (TATI), and other indicators at the L3 level, along with body shape index (BSI) and additional indicators based on WC, were obtained. The relationships between these indicators, response, PFS, OS, and their interconnections were examined.

Results: A total of 145 SCLC patients who received immunotherapy were identified, of whom 133 met the inclusion criteria. In univariate analysis, a BMI≥28 kg/m^2 was associated with a PFS advantage (HR 0.42, p=0.04), but this trend vanished in multivariate analysis. Body measurements exhibited stronger correlations with adipose tissue content, with BSI showing the highest correlation with muscle. In multivariate analysis, lower BSI was associated with poorer OS (HR 1.79, p=0.02). The association between muscle composition and prognosis was robust in univariate analysis but dissipated in multivariate analysis. However, accounting for a high TATI background significantly heightened the adverse effect of SMI on prognosis in the multivariate model.

Conclusion: No clear association between BMI and SCLC immunotherapy prognosis was observed. However, high adiposity exacerbated the adverse effects of sarcopenia in SCLC immunotherapy, and BSI demonstrated potential as a straightforward prognostic measure.

KEYWORDS

small cell lung cancer, immunotherapy, body mass index, sarcopenia, obesity

1 Introduction

Small cell lung cancer (SCLC) represents a neuroendocrine tumor, comprising approximately 13%-15% of all lung cancers, and remains one of the most lethal malignancies. It is highly aggressive with a poor prognosis, and over 60% of patients are diagnosed in the extensive stage (1). Etoposide plus platinum is the standard treatment for SCLC. In the chemotherapy era, the median survival for SCLC was a mere 7 months, with a 2-year survival rate of 7-8% (2). Since 2019, immune checkpoint inhibitors (ICIs) have gained approval as the first-line treatment for extensive-stage small cell lung cancer (ES-SCLC). Although the addition of ICIs has significantly extended survival in SCLC patients, these improvements are underwhelming compared to those seen in non-small cell lung cancer (NSCLC), with ICIs extending median overall survival (OS) in SCLC by only 2-4.5 months (3). Nevertheless, there has been a notable increase in the number of patients surviving beyond 3 years compared to the chemotherapy (4). Identifying potential beneficiaries of ICIs in SCLC and intervening to enhance their benefits remain pressing challenges.

Recently, contrary to the adverse effects of obesity on tumor progression in many preclinical studies, several studies have suggested that obese or high body mass index (BMI) cancer patients may derive greater benefits from ICIs, which is called the "obesity paradox" (5). Research indicates that overweight and obese NSCLC patients undergoing ICIs exhibit better progression-free survival (PFS) and OS than their non-obese counterparts, with a more pronounced trend in patients expressing positive programmed cell death ligand-1 (PD-L1) (6). Similar trends have been observed in malignant melanoma (7, 8). However, some studies have failed to establish a link between BMI and the prognosis of immunotherapy (9, 10), highlighting BMI's limitations as a measure that doesn't capture specific body composition. Moreover, whether BMI is associated with the prognosis of immunotherapy for SCLC remains unexplored.

In recent years, there has been significant interest in obtaining specific body composition through computed tomography (CT) images. Multiple studies have highlighted the association between subcutaneous or visceral adipose tissue and the prognosis of immunotherapy (11, 12). Additionally, the evaluation of skeletal muscle at the L3 level is a well-established method for assessing sarcopenia (13). Chaunzwa et al. studied the impact of L3 level skeletal muscle and adipose tissue composition on the prognosis of advanced NSCLC immunotherapy using CT imaging, and found that a reduction in skeletal muscle content and an increase in the density of subcutaneous adipose tissue (SAT) were associated with worse prognosis (14). There are also some small-sample studies that have shown that CT-measured reductions in skeletal muscle are detrimental to the prognosis of immunotherapy for advanced NSCLC (15, 16). However, research into immunotherapy for SCLC is still quite scarce in this field. This study aims to investigate the correlation between body composition, as determined through CT imaging, and immunotherapy prognosis in ES-SCLC. In consideration of practical applicability, we have also incorporated new anthropometric indicators based on waist circumference (WC) with the hope of identifying a more suitable indicator than BMI to guide the management of ES-SCLC patients.

2 Methods

2.1 Patient population

We conducted a retrospective analysis of 145 patients with SCLC who underwent immune checkpoint inhibitor (ICI) therapy at Zhongnan Hospital of Wuhan University from April 2019 to April 2023. Inclusion criteria comprised pathologically confirmed SCLC, CT-confirmed extensive-stage disease, receipt of at least one anti-programmed cell death protein 1 (PD-1) or anti-PD-L1 treatment, and the availability of abdominal CT or positron emission tomography/computed tomography (PET/CT) within two months before or after the first immunotherapy. Exclusion criteria included lung adenocarcinoma transformation into small cell lung cancer (n=3), unknown baseline time of immunotherapy (n=7), and loss of follow-up (n=2). Ultimately, 133 patients were included in the study.

Clinical information, including gender, age, height, weight, Eastern Cooperative Oncology Group performance status (ECOG PS), stage, metastatic organs, ICI types, and previous treatment, was collected from electronic medical records. Response, PFS, and OS were obtained through electronic medical records and telephone follow-up. Response was evaluated based on RECIST V.1.1, with a patient considered to have achieved a response if they attained complete response (CR) or partial response (PR). Our study

included 4 patients who achieved CR, while efficacy evaluation was not available for 11 patients. PFS was defined as the time from the treatment start to progression or death. OS was defined as the time from the treatment start to death or last follow-up.

2.2 Measurement of WC and body composition

Analysis of non-contrasted PET-CT or CT images was performed using 3D slicer (USA, Version 5.0.2) (17). The entire image file was uploaded to the software, and the L3-L4 level of the CT image was determined (Figure 1). Muscle tissue was defined with a threshold of -29 to +150 HU, SAT with a threshold of -190 to -30 HU, and visceral adipose tissue (VAT) with a threshold of -150 to -50 HU. Two researchers, trained in imaging, independently mapped each patient's body composition at the L3 level and WC at the L3-L4 disc level. The area of each section and skeletal muscle density (SMD) were computed using the Segment Geometry plugin (18). Every image is verified by professional radiologist.

2.3 Determination of the cut-off value

BMI is calculated as weight (kg)/height $(m)^2$. To address variations in body shape specific to Asians and Caucasians (19), we adopted Chinese adult classifications: Normal < 24 kg/m^2, 24 kg/m^2 ≤ Overweight < 28 kg/m^2, and Obese ≥ 28 kg/m^2. WC is considered a superior indicator of central obesity, with high WC defined as ≥ 0.9m for males and ≥ 0.8m for females (20). Waist-to-Height Ratio (WHtR), representing the ratio of WC to height, is considered high when WHtR > 0.5. Other novel anthropometric indicators, namely Relative Fat Mass Index (RFM), Body Shape Index (BSI), Body Roundness Index (BRI), and Weight-Adjusted-Waist Index (WWI), provide a more nuanced reflection of body fat and total fat mass distribution (21). As there are no established reference boundaries for Asians presently, we classified them into quartiles (refer to Supplementary Table S1 for formulas and boundary values).

Skeletal Muscle Index (SMI) is computed as muscle area (cm^2)/height $(m)^2$. According to the international consensus on sarcopenia diagnosis (13), SMI<55 cm^2/m^2 for males and SMI<39 cm^2/m^2 for females defines sarcopenia. SMD, a measure of muscle attenuation associated with myosteatosis, was classified using quartiles. Skeletal Muscle Gauge (SMG), a composite index integrating SMI and SMD, is calculated as SMI multiplied by SMD and considered low when SMG<1475, as per Shachar et al.'s study (22, 23), Lean Body Mass (LBM) is estimated using the L3 muscle area (24), while VAT Index (VATi) and SAT Index (SATi) are standardized VAT and SAT areas, respectively, and Total Adipose Tissue Index (TATI) is the sum of VAT Index and SAT Index, all classified by quartiles.

2.4 Statistical analysis

Continuous variables were compared between groups using the student-t test or Mann-Whitney U test, and categorical variables were compared using the χ^2 test. PFS and OS were assessed using the Kaplan-Meier (KM) method, with group comparisons performed using the log-rank test. Univariate and multivariate Cox regression models were employed to estimate associations between BMI, anthropometric measures, and body composition with survival, adjusting for covariates such as age, gender, stage, ICI line, and ICI types. Logistic regression models were established to evaluate the association between each index and response incidence. Spearman correlation analysis was used to assess the correlation between various indicators. Interactions between TATI with SMI and SMG were calculated following Källberg et al.'s method (25). The main criterion for determining whether there is an interaction is based on the p-value and confidence interval (CI) of the interaction term (SMG×TATI or SMI×TATI), and stratified analysis was conducted in the multivariate model to control for variables. Statistical analyses were carried out using R V.4.2.2.

3 Results

3.1 Patient characteristics

A total of 133 patients were included in the analysis (Table 1), with the last follow-up date on October 1, 2023, and a median follow-up time of 552 days. At the last follow-up, 48 patients were

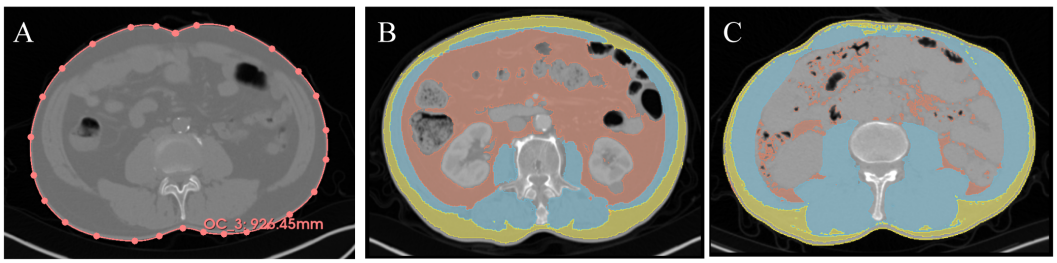

FIGURE 1
Representative imaging contour results. Yellow = SAT, Red = VAT, Blue = muscle. **(A)** Waist circumference measurement, the red line represents the waist circumference. **(B)** Representative low SMI + high TATI. **(C)** Representative high SMI + low TATI. SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue; SMI, skeletal muscle index; TATI, total adipose tissue index.

TABLE 1 Patient baseline characters.

	Overall (N=133)	Normal (N=82)	Overweight (N=40)	Obese (N=11)	P value
Age, Mean (SD)	63.1 (9.49)	63.0 (8.81)	64.4 (9.40)	59.4 (13.9)	0.288
Gender, n (%)					0.465
Male	114 (85.7%)	70 (85.4%)	33 (82.5%)	11 (100%)	
Female	19 (14.3%)	12 (14.6%)	7 (17.5%)	0 (0.00%)	
PS Score, n (%)					0.218
0-1	104 (78.2%)	60 (73.2%)	35 (87.5%)	9 (81.8%)	
≥2	29 (21.8%)	22 (26.8%)	5 (12.5%)	2 (18.2%)	
Clinical Stage, n (%)					0.873
III	21 (15.8%)	13 (15.9%)	7 (17.5%)	1 (9.09%)	
IV	112 (84.2%)	69 (84.1%)	33 (82.5%)	10 (90.9%)	
Metastatic Organs, n (%)					0.763
0	21 (15.8%)	13 (15.9%)	7 (17.5%)	1 (9.09%)	
1-2	65 (48.9%)	38 (46.3%)	22 (55.0%)	5 (45.5%)	
≥3	47 (35.3%)	31 (37.8%)	11 (27.5%)	5 (45.5%)	
ICI Line, n (%)					0.070
First line	93 (69.9%)	60 (73.2%)	23 (57.5%)	10 (90.9%)	
Second and posterior line	40 (30.1%)	22 (26.8%)	17 (42.5%)	1 (9.09%)	
ICI type, n (%)					0.419
PD-L1	61 (45.9%)	40 (48.8%)	15 (37.5%)	6 (54.5%)	
PD-1	72 (54.1%)	42 (51.2%)	25 (62.5%)	5 (45.5%)	
Waist Circumference, Mean (SD)	84.9 (11.2)	79.5 (9.30)	91.6 (6.86)	100 (8.57)	<0.001
BMI, Mean (SD)	23.0 (3.43)	20.8 (2.02)	25.7 (1.11)	29.4 (1.15)	<0.001
Sarcopenic, n (%)					<0.01
No	39 (29.3%)	18 (22.0%)	13 (32.5%)	8 (72.7%)	
Yes	94 (70.7%)	64 (78.0%)	27 (67.5%)	3 (27.3%)	

still alive. The median PFS was 169 days, and the median OS was 331 days. Of the total, 62 patients achieved CR or PR, resulting in an Overall Response Rate (ORR) of 50.82%. The median time from baseline CT to immunotherapy initiation was 8 (IQR 4-24) days.

Patients had a median age of 64, with a majority being male (85.7%). The majority of patients were classified as stage IV (84.2%) based on TNM staging, and overall health was generally favorable. Chemo-immunotherapy was the predominant first-line treatment (69.9%), with a similar distribution between anti-PD-1 and anti-PD-L1 treatments. Sarcopenia was prevalent at baseline, affecting 70.7% of patients, with higher incidence observed in those with normal and overweight BMI compared to obese individuals.

3.2 Associations with BMI

We utilized the KM method to analyze survival differences among BMI subgroups (Supplementary Figure S1). Overall, no significant differences were observed in PFS and OS among the subgroups. However, in pairwise comparisons, PFS was significantly better in the obese group compared to the overweight group (p-value=0.04). In univariate analysis, the response in the overweight group was significantly worse than the normal group (OR 0.43, 95% CI 0.18 to 0.95, p-value=0.04), and the PFS in the obese group was significantly better than the overweight group (HR 0.42, 95% CI 0.19 to 0.96, p-value=0.04). However, these differences were not significant in multivariate analysis (Supplementary Table S2).

3.3 Correlation between each indicator

Given the inclusion of numerous anthropometric indicators, in addition to commonly used BMI, in this study, other indicators also show potential for clinical application. We aimed to explore the correlation between these indicators and body composition (Figure 2). After excluding indicators with direct calculation

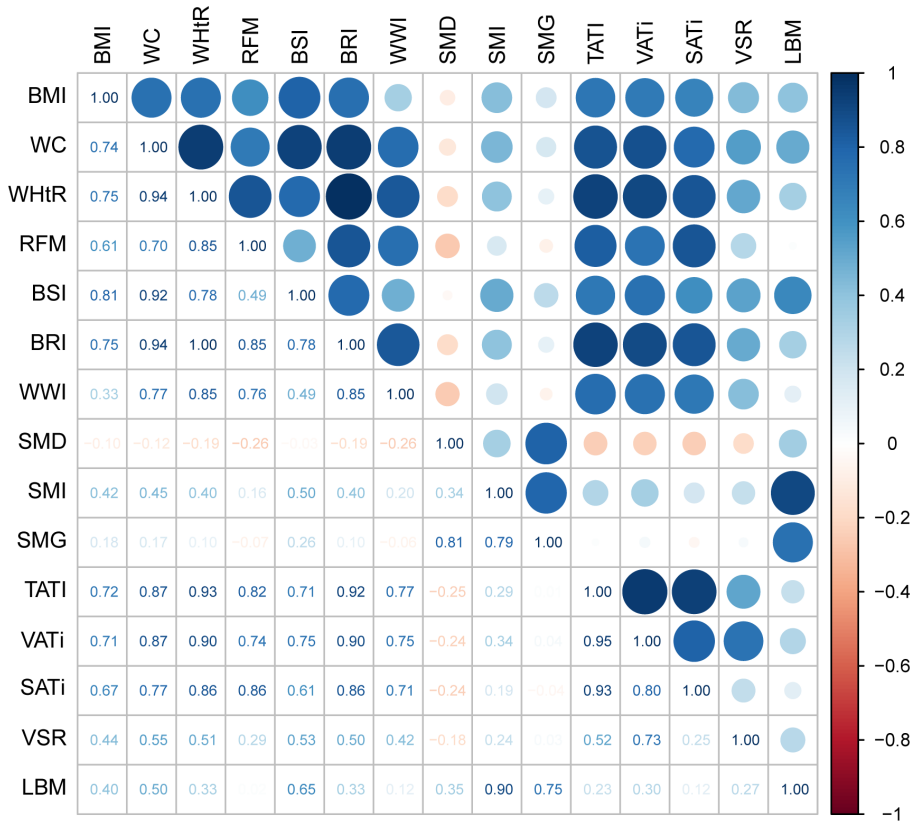

FIGURE 2
The heatmap showing the correlation between various anthropometric indicators and body composition. The numbers in the chart represent the correlation coefficient. A correlation coefficient>0.7 is considered a strong correlation, while 0.3<correlation coefficient ≤ 0.7 is considered a moderate correlation, and correlation coefficient<0.3 is considered a weak correlation. BMI, body mass index; WC, waist circumference; WHtR, waist-to-height ratio; RFM, relative fat mass index; BSI, body shape index; BRI, body roundness index; WWI, weight-adjusted-waist index; SMI, skeletal muscle index; SMD, skeletal muscle density; SMG, skeletal muscle gauge; TATI, total adipose tissue index; VATi, visceral adipose tissue index; SATi, subcutaneous adipose tissue index; VSR, visceral to subcutaneous adipose tissue area ratio; LBM, lean body mass.

relations, we observed that all anthropometric measures, including BMI, were strongly associated with adipose composition and weakly associated with muscle composition. The anthropometric indicator with the strongest correlation with muscle tissue is BSI, with a correlation coefficient of 0.50 with SMI and 0.65 with LBM. Additionally, BSI maintains a strong correlation with TATI (correlation coefficient 0.71).

3.4 Associations with anthropometric measures

As the clinical significance of new anthropometric indicators in cancer prognosis remains unclear, univariate and multivariate analyses were conducted with high quartile and low quartile as cut-off values, in addition to WC and WHtR. In univariate analysis, no significant associations were found between anthropometric measures and response, PFS, or OS. However, after adjusting for covariates, a poorer response was observed in patients with a lower WWI (OR 0.34, 95% CI 0.11 to 0.97, p-value=0.047), and a poorer OS was observed in patients with a lower BSI (HR 1.79, 95% CI 1.09 to 2.94, p-value=0.02) (Supplementary Table S3).

3.5 Associations with body composition measures

In univariate analysis, lower SMI and SMG were associated with worse response (SMI: OR 0.35, 95% CI 0.15 to 0.76, p-value=0.01; SMG: OR 0.4, 95% CI 0.18 to 0.84, p-value=0.02) and OS (SMI: HR 2.00, 95% CI 1.20 to 3.34, p-value=0.01; SMG: HR 1.63, 95% CI 1.06 to 2.51, p-value=0.03), and lower SMG was also associated with worse PFS (HR 1.73, 95% CI 1.18 to 2.55, p-value=0.01). Higher LBM was associated with better response (OR 2.95, 95% CI 1.29 to 7.17, p-value=0.01) and OS (HR 0.58, 95% CI 0.34 to 0.98, p-value=0.04). However, in multivariate analysis, none of these associations remained significant. Both higher (OR 0.29, 95% CI 0.10 to 0.80, p-value=0.02) and lower visceral to subcutaneous adipose tissue area ratio (VSR) (OR 0.20, 95% CI 0.05 to 0.70, p-value=0.01) were associated with poorer responses, suggesting that a moderate range of VSR may be more beneficial to treatment. Similar to new anthropometric indicators, univariate and multivariate analyses were conducted with high quartile and low quartile as cut-off values for VSR and LBM (Table 2).

10.3389/fimmu.2024.1439877

TABLE 2 Univariate and multivariate analyses assess the association between body composition measures with response, PFS, and OS.

Univariate analysis			
Response (n=122)	OR	95% CI	P value
SMI (Sarcopenic VS Non-sarcopenic)	0.35	0.15 to 0.76	0.01*
SMD (Low VS High)	0.80	0.35 to 1.83	0.60
SMG (Low VS High)	0.40	0.18 to 0.84	0.02*
TATI (High VS Low)	0.96	0.42 to 2.17	0.92
VATi (High VS Low)	0.81	0.36 to 1.81	0.60
SATi (High VS Low)	1.24	0.55 to 2.84	0.61
VSR (Low VS High)	0.57	0.19 to 1.55	0.28
VSR (High VS Low)	0.52	0.22 to 1.18	0.12
LBM (Low VS High)	0.56	0.24 to 1.28	0.18
LBM (High VS Low)	2.95	1.29 to 7.17	0.01*
PFS (n=133)	HR	95% CI	P value
SMI (Sarcopenic VS Non-sarcopenic)	1.51	0.99 to 2.31	0.06
SMD (Low VS High)	1.46	0.96 to 2.21	0.08
SMG (Low VS High)	1.73	1.18 to 2.55	0.01*
TATI (High VS Low)	1.10	0.45 to 2.68	0.84
VATi (High VS Low)	0.71	0.45 to 1.13	0.15
SATi (High VS Low)	0.89	0.58 to 1.39	0.62
VSR (Low VS High)	1.07	0.64 to 1.79	0.81
VSR (High VS Low)	1.26	0.82 to 1.92	0.29
LBM (Low VS High)	1.16	0.75 to 1.80	0.50
LBM (High VS Low)	0.67	0.43 to 1.05	0.08
OS (n=133)	HR	95% CI	P value
SMI (Sarcopenic VS Non-sarcopenic)	2.00	1.20 to 3.34	0.01*
SMD (Low VS High)	1.47	0.93 to 2.32	0.10
SMG (Low VS High)	1.63	1.06 to 2.51	0.03*
TATI (High VS Low)	0.87	0.46 to 1.67	0.69
VATi (High VS Low)	0.68	0.40 to 1.14	0.14
SATi (High VS Low)	0.84	0.51 to 1.40	0.51
VSR (Low VS High)	0.99	0.55 to 1.78	0.97
VSR (High VS Low)	1.26	0.79 to 2.01	0.34
LBM (Low VS High)	1.55	0.97 to 2.48	0.07
LBM (High VS Low)	0.58	0.34 to 0.98	0.04*
Multivariable analysis			
Response (n=122)	OR	95% CI	P value
SMI (Sarcopenic VS Non-sarcopenic)	0.72	0.23 to 2.13	0.55
SMD (Low VS High)	1.14	0.39 to 3.47	0.81
SMG (Low VS High)	0.52	0.18 to 1.44	0.21
TATI (High VS Low)	1.08	0.37 to 3.13	0.88
VATi (High VS Low)	0.56	0.19 to 1.58	0.28
SATi (High VS Low)	1.32	0.46 to 3.98	0.62
VSR (Low VS High)	0.20	0.05 to 0.70	0.01*
VSR (High VS Low)	0.29	0.10 to 0.80	0.02*
LBM (Low VS High)	0.57	0.19 to 1.67	0.30
LBM (High VS Low)	1.25	0.43 to 3.73	0.69
PFS (n=133)	HR	95% CI	P value
SMI (Sarcopenic VS Non-sarcopenic)	1.11	0.68 to 1.81	0.67
SMD (Low VS High)	1.49	0.93 to 2.39	0.10
SMG (Low VS High)	1.54	0.99 to 2.41	0.06
TATI (High VS Low)	0.78	0.25 to 2.45	0.68
VATi (High VS Low)	0.70	0.44 to 1.12	0.14
SATi (High VS Low)	0.83	0.52 to 1.33	0.44
VSR (Low VS High)	1.14	0.67 to 1.96	0.63
VSR (High VS Low)	1.23	0.80 to 1.90	0.35
LBM (Low VS High)	1.17	0.74 to 1.84	0.50
LBM (High VS Low)	0.92	0.58 to 1.46	0.72
OS (n=133)	HR	95% CI	P value
SMI (Sarcopenic VS Non-sarcopenic)	1.40	0.77 to 2.54	0.27
SMD (Low VS High)	1.54	0.93 to 2.55	0.09
SMG (Low VS High)	1.55	0.97 to 2.49	0.07
TATI (High VS Low)	0.75	0.38 to 1.47	0.40
VATi (High VS Low)	0.69	0.41 to 1.18	0.18
SATi (High VS Low)	0.74	0.44 to 1.24	0.26
VSR (Low VS High)	1.21	0.66 to 2.22	0.54
VSR (High VS Low)	1.37	0.85 to 2.20	0.20
LBM (Low VS High)	1.36	0.83 to 2.23	0.22
LBM (High VS Low)	0.87	0.49 to 1.56	0.64

#Adjusted for age, gender, stage, ICI line and ICI types. *P ≤ 0.05.
OS, overall survival; PFS, progression free survival.

3.6 Interaction between SMI and TATI

Examining potential interactions between muscle composition and adipose composition, we first explored the interaction between SMG and TATI, but no significant interaction was found (Supplementary Tables S4, S5). Despite the significant p-value, when combined with the CI and stratified analysis results, we do not find an interaction between SMG and TATI in our cohort. Subsequently, we examined the interaction between SMI and TATI,

10.3389/fimmu.2024.1439877

finding that the interaction term SMI × TATI was significant for PFS (HR 0.93, 95% CI 0.89 to 0.98, p-value=0.0034) but not for response and OS (Supplementary Table S6). Additionally, we explored whether there was an additive interaction between these variables, but no statistically significant additive interaction effect was found. Subsequently, we controlled SMI and TATI respectively in the multivariate analysis to assess whether the relationship between another indicator and response, PFS, and OS changed (Table 3). We observed that when high SMI was controlled, PFS significantly improved with high TATI (HR 0.39, 95% CI 0.16 to 0.99, p-value=0.046). Conversely, when high TATI was controlled, the negative impact of low SMI on PFS (HR 4.21, 95% CI 1.01 to 17.57, p-value=0.049) and OS (HR 10.96, 95% CI 2.36 to 50.90, p-value=0.0022) became significantly greater. Finally, we employed the KM method to examine survival differences among subgroups with different SMI and TATI combinations. Among all subgroups, the Low SMI + High TATI group exhibited the worst PFS and OS, with the largest difference observed when compared to the High SMI + Medium TATI group (Figure 3).

TABLE 3 Stratified analysis of the association between SMI and TATI with response, PFS, and OS.

Response (n=122)	OR	95% CI	P value
High SMI			
TATI (High VS Low)	1.04	0.76 to 1.44	0.79
Low SMI			
TATI (High VS Low)	0.92	0.70 to 1.19	0.51
High TATI			
SMI (Low VS High)	0.76	0.45 to 1.28	0.31
Low TATI			
SMI (Low VS High)	0.92	0.73 to 1.17	0.50
PFS (n=133)	**HR**	**95% CI**	**P value**
High SMI			
TATI (High VS Low)	0.39	0.16 to 0.99	0.049*
Low SMI			
TATI (High VS Low)	1.28	0.67 to 2.47	0.46
High TATI			
SMI (Low VS High)	4.21	1.01 to 17.57	0.05*
Low TATI			
SMI (Low VS High)	0.87	0.47 to 1.60	0.65
OS (n=133)	**HR**	**95% CI**	**P value**
High SMI			
TATI (High VS Low)	0.48	0.16 to 1.40	0.18
Low SMI			
TATI (High VS Low)	1.12	0.57 to 2.21	0.73
High TATI			
SMI (Low VS High)	10.96	2.36 to 50.90	<0.01**
Low TATI			
SMI (Low VS High)	1.16	0.55 to 2.42	0.70

Adjusted for age, gender, stage, ICI line and ICI types. *P ≤ 0.05; **P<0.01.

4 Discussion

To the best of our knowledge, this is the first study providing a comprehensive analysis of the association between body composition, anthropometric indexes, and the prognosis of immunotherapy in patients with ES-SCLC. In the era of chemotherapy, prior studies investigated the relationship between body composition, BMI, and the efficacy and prognosis of small-cell lung cancer (SCLC). While sarcopenia, diagnosed at the L3 levels on CT, has been linked to a poorer prognosis for SCLC (26, 27), the association with BMI remains uncertain. Some studies suggested a negative impact of low BMI on SCLC prognosis (28), while others reported complex and inconclusive associations, with trends toward better prognosis in patients with BMI >28kg/m² and weight loss (WL) ≤5% (29). There is a lack of evidence to suggest a link between WC and its newer variants and the prognosis of SCLC. In the era of immunotherapy, there is limited research, with only one pan-cancer study incorporating three SCLC patients receiving immunotherapy, yielding no conclusive results on BMI (30). Generally, SCLC has received less attention in anthropometric studies. As such the disease is lacking anthropometric biomarkers and presenting a significant clinical challenge.

In numerous preclinical studies, obesity has been correlated with tumor progression, attributed to its role in fostering a chronic inflammatory state and an immunosuppressive tumor immune microenvironment (31). Notably, obesity induces T-cell depletion, as evidenced by increased expression of PD-1, T cell immunoglobulin and mucin domain-3 (TIM-3), and lymphocyte activation gene-3 (LAG-3) in tumor-bearing mice with diet-induced obesity (DIO) (8, 32). However, the advent of immunotherapy has altered this scenario. ICIs counteract T-cell dysfunction by targeting PD-1 or PD-L1. Anti-PD-1 treatment for DIO mice in preclinical studies reversed immunosuppression in the tumor microenvironment (TME), with DIO mice exhibiting enhanced efficacy compared to the control group (33). Some clinical studies also indicated that patients with higher BMI derive more benefits from immunotherapy, termed the "obesity paradox" (6, 8). The debate around the "obesity paradox" centers on the evaluation index of BMI (5). Despite its clinical ubiquity, BMI is a relatively crude measure that inadequately reflects specific body composition. In our study, BMI demonstrated a weak correlation with muscle composition, while skeletal muscle has been established as a prognostic factor in various cancers (34). Recent studies have sought to elucidate the "obesity paradox" using imaging measurements. Young et al. (9), investigating the prognosis of immunotherapy for malignant melanoma, found no association between BMI and clinical outcomes, suggesting that the link between body composition and improved clinical outcomes is modest. Lee et al. (11), on the other hand, proposed that visceral fat might explain the "obesity paradox," with its prognostic impact

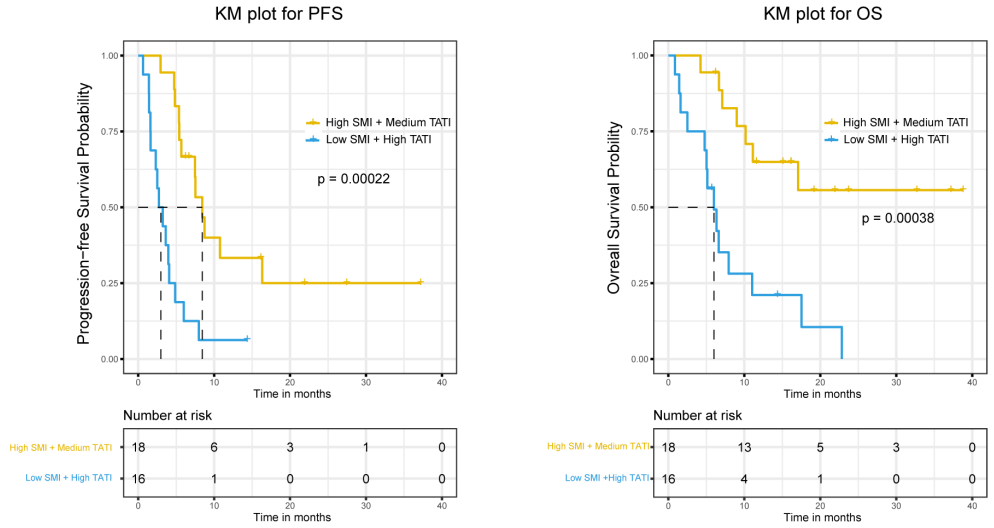

FIGURE 3
The Kaplan-Meier curves of PFS and OS were compared among different SMI and TATI combinations. SMI, skeletal muscle index; TATI, total adipose tissue index; PFS, progression free survival; OS, overall survival.

dependent on the systemic inflammatory state. Discrepancies between these studies may be attributed to differences in race and cut-off points. Although combining body composition and systemic immune-inflammation index (SII) is popular, establishing a causal relationship between the two remains debatable.

While our study focused on different populations and diseases, our findings generally align with those of Young et al. In univariate analysis and KM curves, the obese group exhibited advantages in terms of PFS and OS, but these advantages did not persist in multivariate analysis. Objectively, we did not identify a clear relationship between high BMI and the prognostic benefits of immunotherapy. Existing anthropometric measures, primarily based on height, weight, and waist circumference, are more closely tied to adipose content and less indicative of skeletal muscle. Among the examined anthropometric measures, BSI emerged as the most promising indicator, reflecting both skeletal muscle and adipose content. BSI was also associated with OS in multivariate analysis, though its efficacy as a biomarker requires further validation. Additionally, our study identified intriguing indicators, such as the association of WWI and LBM with response, potentially linked to the distribution of chemotherapeutic drugs (24). Both higher and lower VSRs were associated with worse responses, suggesting that a moderate VSR may confer better therapeutic benefits. Crucially, our data underscore the significance of the skeletal muscle-adipose tissue interaction. The detrimental effects of sarcopenia are significantly exacerbated in the presence of high adipose, consistent with the understanding that sarcopenic obesity portends worse outcomes (24, 35).This effect was more pronounced in SCLC than what Young et al. observed in malignant melanoma. Given SCLC's neuroendocrine nature and diverse tumor syndromes, the interaction and crosstalk between tumor and non-tumor tissues merit consideration. Leptin concentration and the leptin/VAT ratio, indicative of adipokine influence, were associated with prolonged PFS in ES-SCLC patients (36). What's more, anti-growth differentiation factor 15 (GDF-15) combined with anti-PD-1 therapy enhanced anti-PD-1 efficacy (37), as GDF-15 is closely tied to cachexia (38). Skeletal muscle and adipose, functioning as endocrine organs, engage in rich crosstalk in the body (39). Therapies targeting this interaction may not only address metabolic diseases but also enhance immunotherapy efficacy.

Several limitations must be acknowledged in our study. Primarily, being a single-center study introduces potential bias in population characteristics. Notably, our cohort exhibits a significant gender proportion bias, with over 80% of patients being male. The insufficient number of female patients precluded gender-stratified analysis. Moreover, many indicators lack clear-cut criteria, and employing quartiles to establish critical values may be inappropriate. Additional patient characteristics that could impact efficacy, such as immunotherapy-related adverse events and pretreatment weight loss, were not included. The relatively small sample size may affect statistical power, especially during further subgroup analyses. Findings regarding BMI require validation in a larger cohort.

5 Conclusion

In conclusion, our study did not reveal a clear association between BMI and the prognosis of SCLC immunotherapy. However, it reinforced the notion that a high-adipose background amplifies the adverse effects of sarcopenia in the context of SCLC immunotherapy. Notably, BSI emerged as a potential proxy for simple body composition assessment. Given the challenges in visually diagnosing sarcopenic obesity, our study underscores the importance of comprehensive nutritional assessment for cancer patients.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding authors.

Ethics statement

Approval was acquired from the clinical ethics committee of Zhongnan Hospital of Wuhan University (approval number, 2023163K). The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because this is a retrospective study, and all data has been de-identified, so there is no harm to the patients.

Author contributions

RF: Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft. LY: Formal analysis, Visualization, Writing – original draft. SX: Data curation, Investigation, Writing – original draft. YX: Methodology, Writing – original draft. TG: Methodology, Writing – original draft. JG: Data curation, Writing – original draft. JZ: Data curation, Writing – original draft. CX: Supervision, Writing – review & editing. ZL: Conceptualization, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2024.1439877/full#supplementary-material

References

1. Megyesfalvi Z, Gay CM, Popper H, Pirker R, Ostoros G, Heeke S, et al. Clinical insights into small cell lung cancer: Tumor heterogeneity, diagnosis, therapy, and future directions. *CA Cancer J Clin*. (2023) 73:620–52. doi: 10.3322/caac.21785

2. Wang Q, Gümüş ZH, Colarossi C, Memeo L, Wang X, Kong CY, et al. SCLC: epidemiology, risk factors, genetic susceptibility, molecular pathology, screening, and early detection. *J Thorac Oncol*. (2023) 18:31–46. doi: 10.1016/j.jtho.2022.10.002

3. Iams WT, Porter J, Horn L. Immunotherapeutic approaches for small-cell lung cancer. *Nat Rev Clin Oncol*. (2020) 17:300–12. doi: 10.1038/s41571-019-0316-z

4. Paz-Ares L, Chen Y, Reinmuth N, Hotta K, Trukhin D, Statsenko G, et al. Durvalumab, with or without tremelimumab, plus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer: 3-year overall survival update from CASPIAN. *ESMO Open*. (2022) 7:100408. doi: 10.1016/j.esmoop.2022.100408

5. Farag KI, Makkouk A, Norian LA. Re-evaluating the effects of obesity on cancer immunotherapy outcomes in renal cancer: what do we really know? *Front Immunol*. (2021) 12:668494. doi: 10.3389/fimmu.2021.668494

6. Kichenadasse G, Miners JO, Mangoni AA, Rowland A, Hopkins AM, Sorich MJ. Association between body mass index and overall survival with immune checkpoint inhibitor therapy for advanced non-small cell lung cancer. *JAMA Oncol*. (2020) 6:512–8. doi: 10.1001/jamaoncol.2019.5241

7. McQuade JL, Daniel CR, Hess KR, Mak C, Wang DY, Rai RR, et al. Association of body-mass index and outcomes in patients with metastatic melanoma treated with targeted therapy, immunotherapy, or chemotherapy: a retrospective, multicohort analysis. *Lancet Oncol*. (2018) 19:310–22. doi: 10.1016/s1470-2045(18)30078-0

8. Wang Z, Aguilar EG, Luna JI, Dunai C, Khuat LT, Le CT, et al. Paradoxical effects of obesity on T cell function during tumor progression and PD-1 checkpoint blockade. *Nat Med*. (2019) 25:141–51. doi: 10.1038/s41591-018-0221-5

9. Young AC, Quach HT, Song H, Davis EJ, Moslehi JJ, Ye F, et al. Impact of body composition on outcomes from anti-PD1 +/- anti-CTLA-4 treatment in melanoma. *J Immunother Cancer*. (2020) 8(2):e000821. doi: 10.1136/jitc-2020-000821

10. Donnelly D, Bajaj S, Yu J, Hsu M, Balar A, Pavlick A, et al. The complex relationship between body mass index and response to immune checkpoint inhibition in metastatic melanoma patients. *J Immunother Cancer*. (2019) 7:222. doi: 10.1186/s40425-019-0699-5

11. Lee JH, Hyung S, Lee J, Choi SH. Visceral adiposity and systemic inflammation in the obesity paradox in patients with unresectable or metastatic melanoma undergoing immune checkpoint inhibitor therapy: a retrospective cohort study. *J Immunother Cancer*. (2022) 10(8):e005226. doi: 10.1136/jitc-2022-005226

12. He M, Chen ZF, Zhang L, Gao X, Chong X, Li HS, et al. Associations of subcutaneous fat area and Systemic Immune-inflammation Index with survival in patients with advanced gastric cancer receiving dual PD-1 and HER2 blockade. *J Immunother Cancer*. (2023) 11(6):e007054. doi: 10.1136/jitc-2023-007054

13. Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, et al. Definition and classification of cancer cachexia: an international consensus. *Lancet Oncol*. (2011) 12:489–95. doi: 10.1016/s1470-2045(10)70218-7

14. Chaunzwa TL, Qian JM, Li Q, Ricciuti B, Nuernberg L, Johnson JW, et al. Body composition in advanced non-small cell lung cancer treated with immunotherapy. *JAMA Oncol*. (2024) 10:773–83. doi: 10.1001/jamaoncol.2024.1120

15. Nishioka N, Naito T, Notsu A, Mori K, Kodama H, Miyawaki E, et al. Unfavorable impact of decreased muscle quality on the efficacy of immunotherapy for advanced non-small cell lung cancer. *Cancer Med*. (2021) 10:247–56. doi: 10.1002/cam4.3631

16. Tsukagoshi M, Yokobori T, Yajima T, Maeno T, Shimizu K, Mogi A, et al. Skeletal muscle mass predicts the outcome of nivolumab treatment for non-small cell lung cancer. *Med (Baltimore)*. (2020) 99:e19059. doi: 10.1097/md.0000000000019059

17. Fedorov A, Beichel R, Kalpathy-Cramer J, Finet J, Fillion-Robin JC, Pujol S, et al. 3D Slicer as an image computing platform for the Quantitative Imaging Network. *Magn Reson Imaging*. (2012) 30:1323–41. doi: 10.1016/j.mri.2012.05.001

18. Huie JM, Summers AP, Kawano SM. SegmentGeometry: A tool for measuring second moment of area in 3D slicer. *Integr Org Biol*. (2022) 4:obac009. doi: 10.1093/iob/obac009

19. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet*. (2004) 363:157–63. doi: 10.1016/s0140-6736(03)15268-3

20. Li Y, Gui J, Liu H, Guo LL, Li J, Lei Y, et al. Predicting metabolic syndrome by obesity- and lipid-related indices in mid-aged and elderly Chinese: a population-based cross-sectional study. *Front Endocrinol (Lausanne)*. (2023) 14:1201132. doi: 10.3389/fendo.2023.1201132

21. Butt JH, Petrie MC, Jhund PS, Sattar N, Desai AS, Køber L, et al. Anthropometric measures and adverse outcomes in heart failure with reduced ejection fraction: revisiting the obesity paradox. *Eur Heart J*. (2023) 44:1136–53. doi: 10.1093/eurheartj/ehad083

22. Marquardt JP, Roeland EJ, Van Seventer EE, Best TD, Horick NK, Nipp RD, et al. Percentile-based averaging and skeletal muscle gauge improve body composition analysis: validation at multiple vertebral levels. *J Cachexia Sarcopenia Muscle*. (2022) 13:190–202. doi: 10.1002/jcsm.12848

23. Shachar SS, Deal AM, Weinberg M, Williams GR, Nyrop KA, Popuri K, et al. Body composition as a predictor of toxicity in patients receiving anthracycline and taxane-based chemotherapy for early-stage breast cancer. *Clin Cancer Res*. (2017) 23:3537–43. doi: 10.1158/1078-0432.Ccr-16-2266

24. Prado CM, Lieffers JR, McCargar LJ, Reiman T, Sawyer MB, Martin L, et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. *Lancet Oncol*. (2008) 9:629–35. doi: 10.1016/s1470-2045(08)70153-0

25. Källberg H, Ahlbom A, Alfredsson L. Calculating measures of biological interaction using R. *Eur J Epidemiol*. (2006) 21:571–3. doi: 10.1007/s10654-006-9037-6

26. Kim EY, Kim YS, Park I, Ahn HK, Cho EK, Jeong YM. Prognostic significance of CT-determined sarcopenia in patients with small-cell lung cancer. *J Thorac Oncol*. (2015) 10:1795–9. doi: 10.1097/jto.0000000000000690

27. Wang K, Long W, Sima X, Zhao Y, Xiao B, Gulizeba H, et al. Sarcopenia defined by skeletal muscle mass index at the third lumbar vertebra is a prognostic factor for extensive-stage small cell lung cancer patients: a retrospective study. *J Thorac Dis*. (2022) 14:2645–51. doi: 10.21037/jtd-22-782

28. Evcil FY, Önal Ö, Özkan EE. The effect of body mass index on survival in lung cancer. *Nutr Cancer*. (2023) 75:857–66. doi: 10.1080/01635581.2022.2159045

29. Oswalt C, Liu Y, Pang H, Le-Rademacher J, Wang X, Crawford J. Associations between body mass index, weight loss and overall survival in patients with advanced lung cancer. *J Cachexia Sarcopenia Muscle*. (2022) 13:2650–60. doi: 10.1002/jcsm.13095

30. Yeung C, Kartolo A, Holstead R, Moffat GT, Hanna L, Hopman W, et al. No association between BMI and immunotoxicity or clinical outcomes for immune checkpoint inhibitors. *Immunotherapy*. (2022) 14:765–76. doi: 10.2217/imt-2021-0250

31. Quail DF, Dannenberg AJ. The obese adipose tissue microenvironment in cancer development and progression. *Nat Rev Endocrinol*. (2019) 15:139–54. doi: 10.1038/s41574-018-0126-x

32. Wu B, Sun X, Gupta HB, Yuan B, Li J, Ge F, et al. Adipose PD-L1 modulates PD-1/PD-L1 checkpoint blockade immunotherapy efficacy in breast cancer. *Oncoimmunology*. (2018) 7:e1500107. doi: 10.1080/2162402x.2018.1500107

33. Pingili AK, Chaib M, Sipe LM, Miller EJ, Teng B, Sharma R, et al. Immune checkpoint blockade reprograms systemic immune landscape and tumor microenvironment in obesity-associated breast cancer. *Cell Rep*. (2021) 35:109285. doi: 10.1016/j.celrep.2021.109285

34. Martin L, Birdsell L, Macdonald N, Reiman T, Clandinin MT, McCargar LJ, et al. Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. *J Clin Oncol*. (2013) 31:1539–47. doi: 10.1200/jco.2012.45.2722

35. Donini LM, Busetto L, Bischoff SC, Cederholm T, Ballesteros-Pomar MD, Batsis JA, et al. Definition and diagnostic criteria for sarcopenic obesity: ESPEN and EASO consensus statement. *Clin Nutr*. (2022) 41:990–1000. doi: 10.1016/j.clnu.2021.11.014

36. Vita E, Stefani A, Piro G, Mastrantoni L, Cintoni M, Cicchetti G, et al. Leptin-mediated meta-inflammation may provide survival benefit in patients receiving maintenance immunotherapy for extensive-stage small cell lung cancer (ES-SCLC). *Cancer Immunol Immunother*. (2023) 72:3803–12. doi: 10.1007/s00262-023-03533-0

37. Haake M, Haack B, Schäfer T, Harter PN, Mattavelli G, Eiring P, et al. Tumor-derived GDF-15 blocks LFA-1 dependent T cell recruitment and suppresses responses to anti-PD-1 treatment. *Nat Commun*. (2023) 14:4253. doi: 10.1038/s41467-023-39817-3

38. Breit SN, Brown DA, Tsai VW. The GDF15-GFRAL pathway in health and metabolic disease: friend or foe? *Annu Rev Physiol*. (2021) 83:127–51. doi: 10.1146/annurev-physiol-022020-045449

39. Guo L, Quan M, Pang W, Yin Y, Li F. Cytokines and exosomal miRNAs in skeletal muscle-adipose crosstalk. *Trends Endocrinol Metab*. (2023) 34:666–81. doi: 10.1016/j.tem.2023.07.006

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Association of dietary habits with general and abdominal obesity in Korean children and adolescents: cluster analysis of nationwide population survey data

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Introduction: Childhood obesity is a growing global health concern, but few studies have investigated dietary factors specifically related to obesity and abdominal obesity in children and adolescents. Herein, we aimed to identify the dietary factors affecting childhood obesity in Korean children and adolescents.

Methods: Data from the Korea National Health and Nutrition Survey (KNHANES) VIII were analyzed using K-means clustering analysis to identify distinct clusters based on nine variables related to dietary habit, nutritional status, and nutritional education. Multiple logistic regression analysis was used to examine the association between incident obesity risk and the different clusters. We enrolled 2,290 participants aged 6-18 years, and separated them into two distinct clusters; Healthy and Unhealthy Dietary Habit Groups, clusters 1 and 2, respectively.

Results: Cluster 1 was characterized by a lower obesity prevalence, healthier dietary habits (regular breakfast consumption; fruit and vegetable, reduced total energy, and lower protein and fat intakes), and greater nutritional education than Cluster 2. After adjusting for confounders, compared with Cluster 1, Cluster 2 demonstrated a significantly higher prevalence (OR [95% CI]) of both general and abdominal obesity (1.49 [1.05–2.13], p=0.027 and 1.43 [1.09–1.88], p=0.009).

Discussion: Maintaining optimal dietary quality and patterns are crucial to prevent childhood obesity. Further research is warranted to explore specific dietary interventions tailored to different clusters to effectively address childhood obesity.

KEYWORDS

child obesity, diet, lifestyle, nutritional education, clustering analysis

1 Introduction

The World Obesity Atlas 2023 (1) shows a significant increase in the prevalence of obesity, particularly among children and adolescents worldwide; among boys, prevalence is estimated to double from 10% in 2020 to 20% in 2035 whereas, for girls, the prevalence is expected to similarly increase from 8% to 18% (1). This highlights the need for strategies to address the escalating burden of obesity, especially among younger populations, to mitigate long-term health consequences and the associated socioeconomic impacts.

Pediatric obesity not only poses a higher risk of sustained obesity, but also carries future health risks in adulthood that have been well-documented (2). The severity of obesity in children and adolescents is closely linked to a higher risk of metabolic syndrome (MetS) (3). Compared to normal-weight individuals, those who are overweight or obese have a 5 and 23 fold higher risk of MetS, respectively (4). Furthermore, childhood BMI has been associated with risks of diabetes, cancer, and cardiovascular diseases, even independent of adult BMI (5).

The treatment of obesity includes behavioral changes in diet, physical activity, sedentary behaviors, and sleep habits (6). The World Health Organization (WHO) recently suggested that limiting energy intake from total fats and sugars by increasing the consumption of fruits, vegetables, whole grains, and nuts, as well as engaging in regular physical activity, are highly recommended at the individual level for obesity prevention (7). It has further been well-documented that healthy dietary patterns are beneficial for children's health (8, 9). Additionally, unlike in adults, children's dietary habits are highly influenced by familial (parental) (10) and socioeconomic factors (11). As dietary habits are important for the prevention and treatment of childhood obesity, dietary factors that can predict obesity and MetS in Korean children and adolescents need to be identified.

Park et al. (12) previously investigated the association of dietary quality with body mass index (BMI) in obese children, but found no significant associations of dietary patterns and quality with BMI in obese children. However, the authors observed an association of high fat intake with weight gain in this population. Kim et al. (13) observed that children who participated in the school lunch program consumed more appropriate nutrients than those in the non-school lunch and skipping lunch groups. Moreover, they found that the school lunch group was less likely to become obese than the skipping lunch group.

Nonetheless, few studies have investigated dietary factors specifically related to obesity and abdominal obesity in children and adolescents. Therefore, in this study, using the K-means clustering algorithm, we aimed to identify dietary factors that increase the risk of obesity in children and adolescents in the Republic of Korea. Unlike in previous studies, we included various dietary habits, such as breakfast eating, frequency of fruit or vegetable consumption, eating out, proportion of macronutrients, nutritional education, and other demographic factors in order to create a comprehensive background for personalized prediction and management of childhood obesity in the Republic of Korea.

2 Materials and methods

The Korea National Health and Nutrition Examination Survey (KNHANES) is a cross-sectional survey that has been conducted annually by the Korea Centers for Disease Control and Prevention (KCDC) since 1998 to derive a comprehensive understanding of the health and nutritional status of the South Korean population. The KNHANES targets non-institutionalized Korean citizens residing in Korea, and follows a multistage, clustered probability design for sampling; detailed information on the KNHANES is available at: https://knhanes.cdc.go.kr/knhanes/eng. In this study, we used data from the KNHANES VIII (2019–2021). Of the 2,928 KNHANES VIII participants aged 6–18 years, those without anthropometric and dietary behavior data (n = 638) were excluded, and a total of 2,290 participants were included in the final analysis, as shown in the study flowchart in Figure 1. All participants provided written informed consent for the use of their data for research purposes. The study protocol was approved by the institutional review board of the Severance Hospital (approval no. 4-2022-0796).

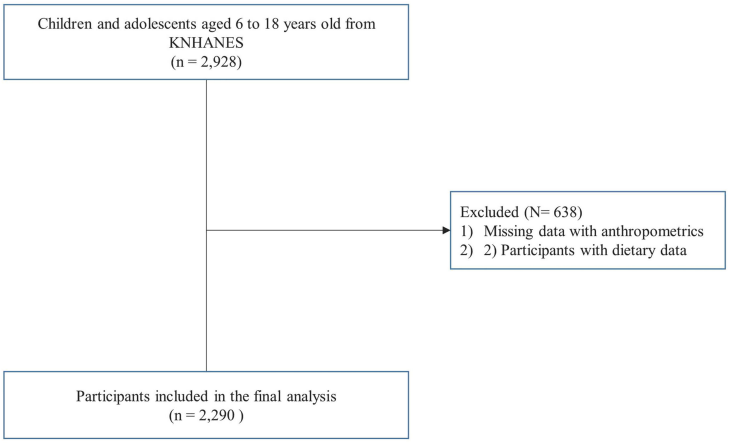

FIGURE 1
Flow chart of the study population.

2.1 Anthropometry and the adiposity index

In the KNHANES VIII, anthropometric measurements, including blood pressure (BP), height, weight, BMI, and waist circumference (WC), were measured by well-trained medical staff. BP was measured three times in the sitting position, and the average of the secondary and tertiary measurements was used in the analysis. Height was measured using a portable stadiometer, with accuracy to the nearest 0.1 cm, while weight was determined using a digital scale, accurate to the nearest 0.1 kg. During measurement, participants were advised to wear light attire and no shoes. WC was measured using a standard measuring tape at the narrowest point of the body, located between the lowest rib and the iliac crest. BMI was calculated by the dividing weight (in kilograms) by the square of height (in meters). The waist-to-height ratio (WHtR) was subsequently determined by dividing each individual's waist circumference (WC) by height. For comparisons, the standard scores (z-scores) for BMI, WC, and WHtR were derived from the KNHANES VIII (2019-2021) using the method described by Kim et el (14), taking into account age and sex. Obesity was defined as BMI values above the 95th percentile, corresponding to age and sex categories following the Korea Centers for Disease Control and Prevention (KCDC) criteria (14). Abdominal obesity was defined as a WC that exceeded the 90th percentile according to age- and sex-specific criteria (15). Abdominal obesity based on WHtR was defined as WHtR ≥0.5 (16).

2.2 Dietary behaviors and nutritional education assessment

According to a standardized protocol, the dietary behaviors of children and adolescents were assessed by well-trained nutritionists through questionnaires that assessed the following items: breakfast frequency per week in the last year (almost every day, 1-4 times a week, or rarely); frequency of eating out (almost every day, more than once a week, or rarely); experience of nutritional education in the past year (yes/no); frequency of consuming vegetables (excluding kimchi and pickled vegetables), mushrooms, and seaweed in the past year (more than three times a day, once or twice a day, or less than once a day); and frequency of consuming fruits in the past year (>7, 2–6, or <1 time(s) per week). The total calorie intake and grams of carbohydrate, fat, and protein were calculated from the 24-hour dietary recall. The total consumption of carbohydrates, protein, and fat was subsequently converted to energy intake in calories (1 g carbohydrates = 4 kcal; 1 g protein = 4 kcal; and 1 g fat = 9 kcal). The proportion of carbohydrates, protein, and fat intake was calculated as follows: carbohydrate, protein, and fat intake calories/total calorie intake × 100.

2.3 Clustering analysis

K-means was used to form clusters using the nine variables related to dietary habit, nutritional status, and nutritional education (frequency of breakfast consumption, frequency of dining out, experience of nutritional education, frequency of consuming vegetables on average, frequency of consuming fruits on average, total calorie intake, proportion of carbohydrate intake, proportion of protein intake, and proportion of fat intake). The frequency of dietary behaviors was clustered by considering the categorical variables as continuous variables. K-means clustering was then performed on the standardized values to have zero mean and unit variance. Using the silhouette method 18, we determined the optimal number of clusters for dietary habits.

2.4 Statistical analysis

All data are reported as the mean ± standard deviation (SD) for continuous variables, or as frequency (proportion) for categorical variables. To compare the differences between clusters, we conducted independent t-tests for continuous variables and the Fisher's exact test for categorical variables. Linear and logistic regression were applied to determine association between clusters of dietary habits and adiposity for Korean children and adolescents. In the regression analysis, age and sex were adjusted to reduce the confounding effects. Subgroup analysis was performed for age groups (6–12 and 13–18 years) and sex. All statistical analyses were conducted using R version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was set at a p-value of less than 0.05.

3 Results

3.1 Clinical characteristics of the two clusters

Using the K-means clustering algorithm, we produced two clusters from the overall participants (N = 2,290). Each cluster comprised participants with characteristics similar to the nine variables within the cluster. The distribution of the participants and characteristics of the two clusters are shown in Figure 2, Table 1. In total, 706 boys and 694 girls were grouped into Cluster 1 (N = 1,400), whereas 500 boys and 390 girls were grouped into Cluster 2 (N = 890).

Compared with Cluster 2, Cluster 1 was characterized by a higher frequency of breakfast consumption, higher experience of nutritional education, higher consumption of vegetables, higher consumption of fruits, lower intake of total energy, higher intake of carbohydrate proportion, lower intake of protein proportion, and lower intake of fat proportion. Accordingly, Clusters 1 and 2 were designated as the healthy dietary habit group (HDG) and unhealthy dietary habit group (UDG), respectively. Table 1 shows the clinical characteristics of Clusters 1 and 2. Participants in Cluster 1 were younger, more likely to be female, less likely to be obese, and had a lower WC.

3.2 Association of adiposity with clusters

Based on the linear regression analysis, Table 2 shows the independent association of BMI, WC, BMI Z-score, and WHtR Z-score with the clusters. Compared with Cluster 1, Cluster 2 had a

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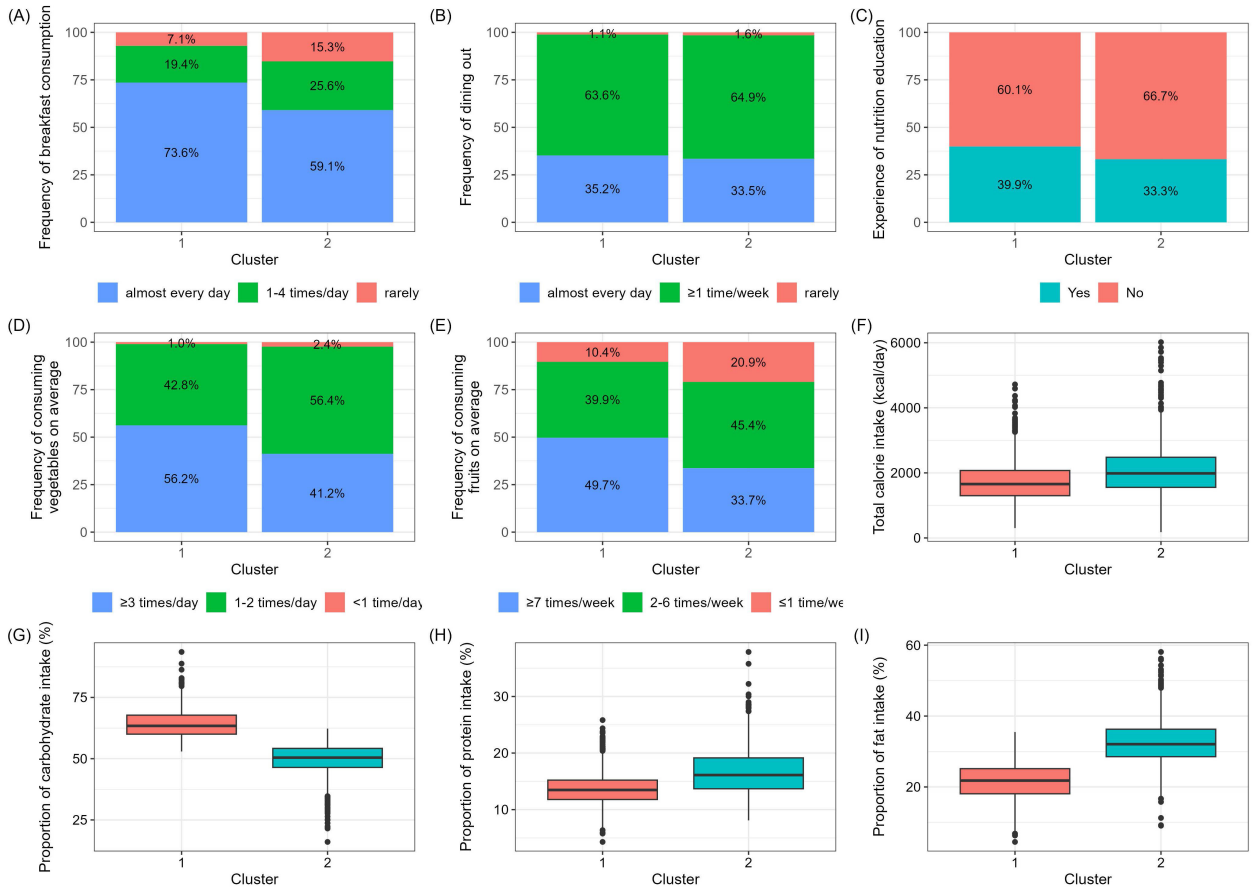

FIGURE 2
Characteristics of the two patient clusters. Data are presented as percentages or box plot (median, IQR). **(A)** Frequency of breakfast consumption, **(B)** Frequency of dining out, **(C)** Experience of nutrition education, **(D)** Average frequency of consuming vegetables, **(E)** Average frequency of consuming fruits, **(F)** Total calorie intake from 24-hour dietary recall, **(G)** Proportion of carbohydrate intake, **(H)** Proportion of protein intake, **(I)** Proportion of fat intake.

significantly higher BMI (β-coefficient and 95% confidence interval [CI], 1.06 [0.70–1.42], $p<0.001$), WC (β and 95% CI, 3.41 [2.38–4.44], $p<0.001$), BMI Z-score (β-coefficient and 95% confidence interval [CI], 0.15 [0.06–0.23], $p<0.001$), and WHtR Z-score (β and 95% CI, 1.15 [0.07–0.23], $p<0.001$). Table 3 shows the cluster-stratified odds ratio (OR) and 95% CI for general obesity and abdominal obesity. Compared with Cluster 1, Cluster 2 had a higher prevalence (OR [95% CI]) of general obesity (1.54 [1.09–2.19], $p=0.015$), abdominal obesity (1.49 [1.14–1.94], $p=0.003$), and abdominal obesity by WHtR (1.35 [1.09-1.66], $p=0.005$). After adjusting for age and sex, Cluster 2 had a significantly higher prevalence (OR [95% CI]) of general obesity (1.49 [1.05–2.13], $p=0.027$), abdominal obesity (1.43 [1.09–1.88], $p=0.009$), and abdominal obesity by WHtR (1.30 [1.05-1.60], $p=0.018$).

Figure 3 presents the results of the age- and sex-stratified subgroup analysis. In both the 6–12 and 13–18 years age groups, Cluster 2 exhibited higher BMI and WC levels than Cluster 1, although the WHtR levels were only significant in the 13-18 years age group. Among boys, compared with Cluster 1, Cluster 2 had higher BMI, WC, and WHtR levels; however, among girls, no significant associations between BMI, WC, WHtR and clusters was observed. Although no significant association was found between general obesity or abdominal obesity and clusters in the 6–12 years age group, in the 13–18 years age group, Cluster 2 exhibited significant trends with a higher prevalence (OR [95% CI]) of general obesity (1.73 [0.99–3.08], $p=0.057$), a significantly higher prevalence of abdominal obesity (1.61 [1.04–2.53], $p=0.034$), and abdominal obesity by WHtR (1.55 [1.09-2.22], $p=0.015$). Among boys, compared with Cluster 1, Cluster 2 had significantly higher prevalence (OR [95% CI]) of general obesity (1.94 [1.24–3.09], $p=0.004$), abdominal obesity (1.49 [1.08–2.06], $p=0.015$), and abdominal obesity by WHtR (1.32 [1.01-1.73], $p=0.039$).

4 Discussion

The present study investigated the association between dietary habits and adiposity indices, while particularly focusing on general and abdominal obesity, among Korean children and adolescents. Overall, our findings indicate that individuals exhibiting HDG, such as increased breakfast consumption, greater exposure to nutritional education, and higher fruit and vegetable intake, demonstrated a lower prevalence of childhood obesity.

TABLE 1 Clinicodemographic characteristics of the entire cohort and the two clusters.

Characteristic	Overall	Cluster 1	Cluster 2	*p*-value
N	2290	1400	890	
Age, years	11.3 ± 3.6	11.0 ± 3.6	11.9 ± 3.6	<0.001
Sex, n (%)				0.008
Male	1,206 (53%)	706 (50%)	500 (56%)	
Female	1,084 (47%)	694 (50%)	390 (44%)	
Body mass index, kg/m^2	19.9 ± 4.3	19.4 ± 4.2	20.5 ± 4.5	<0.001
BMI Z-score	0.00 ± 1.00	-0.05 ± 0.97	0.09 ± 1.05	<0.001
Waist circumference, cm	66.8 ± 12.4	65.5 ± 11.8	68.9 ± 12.9	<0.001
WHtR	0.45 ± 0.06	0.45 ± 0.06	0.45 ± 0.06	0.001
WHtR Z-score	0.00 ± 1.00	-0.06 ± 0.97	0.09 ± 1.03	<0.001
General obesity, n (%)	133 (5.8%)	68 (4.9%)	65 (7.3%)	0.019
Abdominal obesity, n (%)	246 (11%)	129 (9.2%)	117 (13%)	0.004
Abdominal obesity by WHtR, n (%)	443 (19.3%)	245 (17.5%)	198 (22.2%)	0.006

Data are presented as the weighted % (standard error) or weighted mean ± standard error.
General obesity, abdominal obesity and abdominal obesity by WHtR were defined as BMI >95th percentile, WC >90th percentile and WHtR ≥0.5, respectively, using the Korean reference data.
WHtR, waist-to-height ratio.

It is worth noting that 73.6% of children and adolescents in Cluster 1 had breakfast "almost every day," compared with 59.1% in Cluster 2. A meta-analysis comprising 45 observational studies reported an association between breakfast skipping with overweight/obesity and an increased risk of overweight/obesity (17). Another study demonstrated that frequent breakfast skipping was associated with higher odds of MetS in Korean young adults (18). Mengzi et al. (19) Also found that skipping breakfast was positively associated with both the dietary inflammatory index and obesity, and that the association between eating breakfast and BMI was mediated by the dietary inflammatory index. Our findings align with those of these previous studies. Several possible mechanisms may mediate the association of breakfast consumption with metabolic disturbances. Firstly, owing to increased sleep demand, the overnight fasting periods are longer during childhood and adolescence, leading to the overnight depletion of glycogen stores (20). Consequently, given their higher metabolic rates, breakfast consumption becomes crucial for glucose metabolism in children. Furthermore, skipping breakfast can impair insulin function, resulting in higher postprandial plasma glucose levels (21), which potentially explains why a decreased weekly breakfast frequency is associated with a higher risk of insulin resistance in Korean adults without diabetes or prediabetes (22). Secondly, consistent meal patterns can support better appetite control and satiety, thereby reducing the likelihood of overeating or snacking on less nutritious foods (23, 24). Compared with individuals who regularly consume breakfast, young adults who frequently skip breakfast tend to report higher levels of appetite and hunger, decreased feelings of fullness, and increased ghrelin levels (23, 24). Additionally, breakfast skippers often tend to consume larger amounts of food in one sitting during the remainder of the day (25).

In Cluster 1, 52% of individuals ate vegetables more than twice a day, and 41% ate fruit more than six times a week; compared with Cluster 2, these proportions were significantly higher. It has been well-known that fruits and vegetables reduce the risk of chronic health conditions, including obesity (25–27). One systematic review of cohort studies revealed that higher vegetable intake was associated with the lowest risk of weight gain (28), which is consistent with our findings. Thus, we inferred that fruit and vegetable intake aids weight management because these foods are low in energy, but have high fiber and water content, which induces satiety (29). For children aged

TABLE 2 Results of the cluster-stratified linear regression analysis of BMI, WC, BMI Z-score, and WHtR Z-score.

	BMI, Coefficient (95% CI)	*p*-value	WC, Coefficient (95% CI)	*p*-value
Cluster 1	Ref		Ref	
Cluster 2	1.06 (0.70, 1.42)	<0.001	3.41 (2.38, 4.44)	<0.001
	BMI Z-score, Coefficient (95% CI)	*p*-value	WHtR Z-score, Coefficient (95% CI)	*p*-value
Cluster 1	Ref		Ref	
Cluster 2	0.15 (0.06, 0.23)	<0.001	1.15 (0.07, 0.23)	<0.001

BMI, body mass index; WC, waist circumference; WHtR, waist-to-height ratio.

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TABLE 3 Results of the cluster-stratified logistic regression analysis for general and abdominal obesity.

	General obesity, OR (95% CI)	*p*-value	Abdominal obesity, OR (95% CI)	*p*-value	Abdominal obesity by WHtR, OR (95% CI)	*p*-value
Unadjusted						
Cluster 1	Ref		Ref		Ref	
Cluster 2	1.54 (1.09-2.19)	0.015	1.49 (1.14-1.94)	0.003	1.35 (1.09-1.66)	0.005
Age-and sex-adjusted						
Cluster 1	Ref		Ref		Ref	
Cluster 2	1.49 (1.05-2.13)	0.027	1.43 (1.09-1.88)	0.009	1.30 (1.05-1.60)	0.018

General obesity, abdominal obesity and abdominal obesity by WHtR were defined as BMI >95th percentile, WC> 90th percentile and WHtR ≥0.5, respectively, using the Korean reference data. Ref, Reference; WHtR, waist-to-height ratio.

6–11 years, the Dietary Reference Intakes for Koreans (2020) suggested the ideal frequency of fruit and vegetable consumption as once a day (total 300 g/day) and 6–7 cups per day (70 g per cup, total 350 g/day), respectively; for teenagers (12–18 years), vegetables and fruit consumption recommendations were 7–8 cups per day (total 500–550 g/day) and 2–4 times a day (total 200–400 g/day), respectively (30). Although the highest frequency of fruits and vegetables intake were significantly more prevalent in Cluster 1 than in Cluster 2, these were nonetheless actually lower than the abovementioned recommended intake standards. Therefore, we infer that, even if Korean children and adolescents do not meet the intake standards, it is still important to frequently consume fruits and vegetables to prevent obesity, and this can be suggested as a bridging step before aiming to meet the recommended intake standards.

Regarding energy intake, compared with Cluster 2, Cluster 1 consumed less calories, with a higher proportion of carbohydrate and lower proportions of protein and fat. Specifically, compared to the average total energy intake of 1,845 (± 694.1) kcal/day in Cluster 1, Cluster 2 had a significantly higher intake of 2,236 (± 928.5) kcal/day. In Cluster 1, the proportions of carbohydrates, protein, and fat were 63.9%, 13.8%, and 21.6%, respectively, which are all within the recommended Korean nutrient intake standards (carbohydrates,

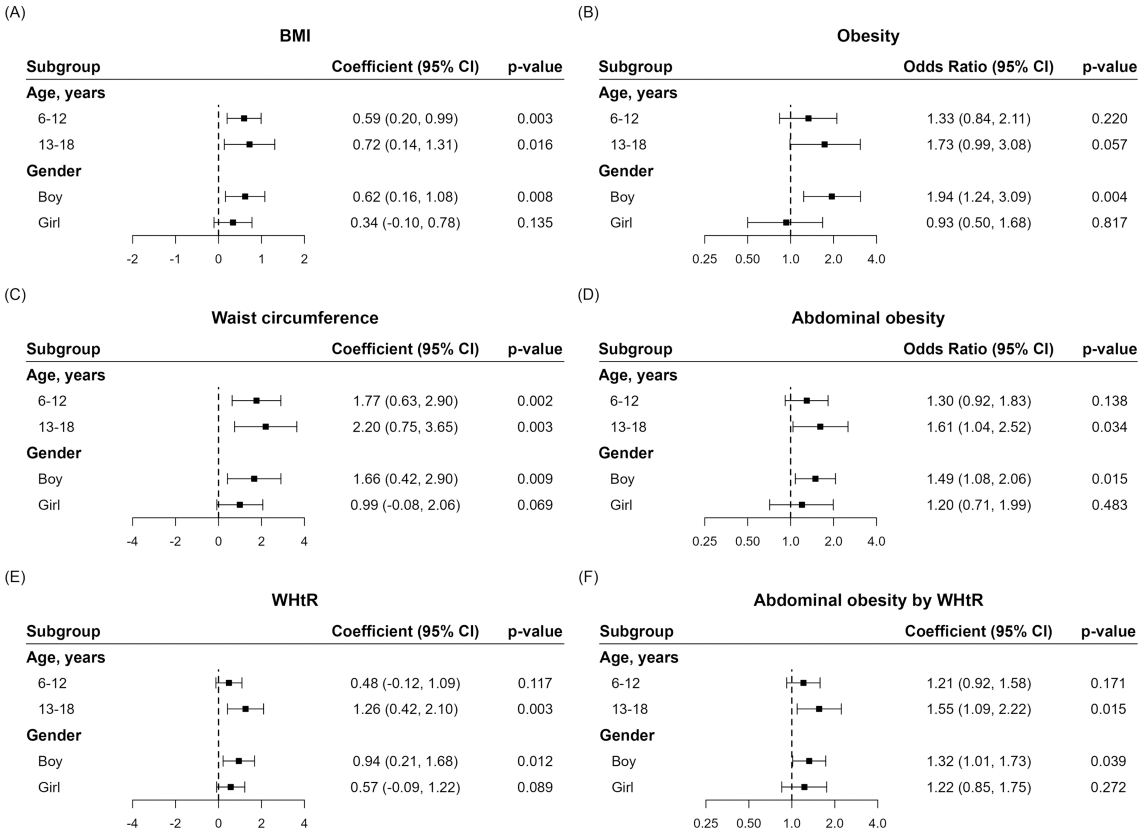

FIGURE 3
Results of subgroup analysis of anthropometric parameters and obesity indices between Clusters 1 and 2. **(A)** BMI, **(B)** Obesity, **(C)** Waist circumference, **(D)** Abdominal obesity, **(E)** WHtR, **(F)** Abdominal obesity by WHtR).

55–65%; protein, 7–20%; and fat, 15–30%) for those aged 6–18 years (30, 31). In contrast, Cluster 2 had lower carbohydrate (48.6%) and higher fat (33.1%) intake proportions compared to the national standards. These findings may be associated with the higher consumption of fruits and vegetables in Cluster 1. Foods high in fat, such as meat or fried fast food, are also commonly associated with childhood obesity (31).

Furthermore, we observed that, compared with Cluster 2, Cluster 1 comprised a greater number of children and adolescents who received nutritional education. School-based interventions can effectively reduce the BMI of children (32) and, when implemented in the home, can even improve the BMI of the parents (33). Moreover, this intervention was conducted with only preschool children and favored the prevention of overweight/obesity (34). Nutritional education can be an effective intervention among children as it increases awareness about the importance of food and its impact on overall well-being, which thereby affects overall dietary behaviors. A study found that adolescents who received nutritional education consumed more vegetables and fruits and skipped breakfast less often (35).

In the subgroup analysis, the difference in the prevalence of obesity between the two clusters was markedly evident in a specific age group (13-18 years) and sex (boys). The 13–18 years age group is notable as it is the timepoint at which Korean girls (12.7 years) and boys (13.8 years) reach puberty (36). Obesity occurs during this transitional period at a higher rate (37) because of metabolic changes, including hormonal impact, lifestyle changes, and pubertal stressors (38). Therefore, it seems important to dedicate adequate care to pubertal diet for obesity prevention.

In addition, compared with Korean female adolescents, Korean male adolescents tend to have higher obesity prevalence (39, 40), which aligns with our study results, as well as global statistical trends in high income countries (41). Some studies consider dietary preference as one of the reasons for this difference, thereby indicating that girls, especially in wealthier nations, might favor foods with lower energy content and higher nutrient density, such as fruits and vegetables, whereas boys tend to opt for more calorie-dense foods, such as meat (42, 43). Moreover, compared to boys, girls often express greater weight-related concerns, including the desire to lose weight, feeling of guilt on overeating, and lower self-esteem (44). Parents also typically exhibit more apprehension regarding their daughters' weight status than that of their sons', with sons often being encouraged to consume more food (45). These social influences on dietary habits may also explain the sex difference.

Our study has several limitations. Firstly, it is important to consider the impact of the COVID-19 pandemic on the collected data, as our data from the KNHANES VIII (2019-2021) coincided with this period. During the pandemic, South Korea experienced lockdowns and school closures, which contributed to changes in physical activity and dietary habits and a rise in childhood obesity rates (46). Indeed, several studies reported an increase in childhood obesity in Korea during the pandemic, particularly among male students, among whom the prevalence of obesity increased more sharply compared to before the pandemic (47, 48). Additionally, fast food and fruit consumption both decreased (48, 49). These findings partially align with our study results, and suggest that the COVID-19 pandemic likely influenced our data. As such, it is essential to consider the complex effects of the pandemic when interpreting our results. Secondly, the frequency of dietary habits was not assessed with regard to specific intake frequencies, but was rather categorized into sections. Thirdly, the specific foods from which nutrients were obtained could not be determined. Finally, it is important to note that the majority of meals consumed by children are provided by families and educational institutions, rather than being based on their own choices. As such, the evaluation of parental eating habits or the quality of school meals could be beneficial additions to future research endeavors. Despite these limitations, our study has noteworthy strengths. This is the first study to utilize a clustering algorithm to identify dietary behaviors that affect childhood obesity within a large, representative Korean population. By examining nine key dietary variables across distinct clusters, we paved the way for the development of personalized interventional strategies.

In conclusion, distinct clusters that represent different childhood obesity-associated dietary habits were identified. Individuals with healthier dietary behaviors, including increased breakfast consumption, greater exposure to nutritional education, and higher fruit and vegetable intake, exhibited a lower prevalence of childhood obesity. It is also imperative to maintain optimal dietary quality and patterns to effectively prevent childhood obesity. This study underscores the significant role of school and family-based nutritional education and dietary interventions for promoting healthier eating habits among children.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: https://knhanes.cdc.go.kr/knhanes/eng.

Ethics statement

All participants provided written informed consent for the use of their data for research purposes. The study protocol was approved by the institutional review board of the Severance Hospital (approval no. 4-2022-0796). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

Y-JY: Writing – original draft, Writing – review & editing. Y-JK: Conceptualization, Investigation, Writing – original draft, Formal analysis, Writing – review & editing. YL: Conceptualization,

Investigation, Writing – original draft, Writing – review & editing. S-JH: Conceptualization, Data curation, Formal analysis, Investigation, Software, Visualization, Writing – original draft, Writing – review & editing. J-WL: Conceptualization, Funding acquisition, Supervision, Validation, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Lobstein T, Jackson-Leach R, Powis J, Brinsden H, Bray M. *World Obesity Atlas 2023*. London, UK: World Obesity Federation (2023). Available at: https://data.worldobesity.org/publications/?cat=19.

2. Geserick M, Vogel M, Gausche R, Lipek T, Spielau U, Keller E, et al. Acceleration of BMI in early childhood and risk of sustained obesity. *New Engl J Med*. (2018) 379:1303–12. doi: 10.1056/NEJMoa1803527

3. Weiss R, Dziura J, Burgert TS, Tamborlane WV, Taksali SE, Yeckel CW, et al. Obesity and the metabolic syndrome in children and adolescents. *N Engl J Med*. (2004) 350:2362–74. doi: 10.1056/NEJMoa031049

4. Lee J-E. Clinical predictive factors for metabolic syndrome in obese children and adolescents. *J Obes Metab Syndrome*. (2016) 25:50–5. doi: 10.7570/kjo.2016.25.2.50

5. Horesh A, Tsur AM, Bardugo A, Twig G. Adolescent and childhood obesity and excess morbidity and mortality in young adulthood-a systematic review. *Curr Obes Rep*. (2021) 10:301–10. doi: 10.1007/s13679-021-00439-9

6. Lister NB, Baur LA, Felix JF, Hill AJ, Marcus C, Reinehr T, et al. Child and adolescent obesity. *Nat Rev Dis Primers*. (2023) 9:24. doi: 10.1038/s41572-023-00435-4

7. Cena H, Calder PC. Defining a healthy diet: evidence for the role of contemporary dietary patterns in health and disease. *Nutrients*. (2020) 12:334. doi: 10.3390/nu12020334

8. Pinho L, Silveira MF, Botelho AC, Caldeira AP. Identification of dietary patterns of adolescents attending public schools. *J Pediatr (Rio J)*. (2014) 90:267–72. doi: 10.1016/j.jped.2013.04.006

9. Smith AD, Emmett PM, Newby PK, Northstone K. Dietary patterns and changes in body composition in children between 9 and 11 years. *Food Nutr Res*. (2014) 8:58. doi: 10.3402/fnr.v58.22769

10. Lee JS, Jin MH, Lee HJ. Global relationship between parent and child obesity: a systematic review and meta-analysis. *Clin Exp Pediatr*. (2022) 65:35–46. doi: 10.3345/cep.2020.01620

11. Hemmingsson E. Early childhood obesity risk factors: socioeconomic adversity, family dysfunction, offspring distress, and junk food self-medication. *Curr Obes Rep*. (2018) 7:204–9. doi: 10.1007/s13679-018-0310-2

12. Park J-S, Choi H-N, Kim J-Y, Ma S-H, Yim J-E. Assessment of dietary quality and nutrient intake of obese children in Changwon area. *J Nutr Health*. (2022) 55:630–41. doi: 10.4163/jnh.2022.55.6.630

13. Kim Y, Son K, Kim J, Lee M, Park KH, Lim H. Associations between school lunch and obesity in korean children and adolescents based on the Korea national health and nutrition examination survey 2017-2019 data: A cross-sectional study. *Nutrients*. (2023) 15:698. doi: 10.3390/nu15030698

14. Kim JH, Yun S, Hwang SS, Shim JO, Chae HW, Lee YJ, et al. The 2017 Korean National Growth Charts for children and adolescents: development, improvement, and prospects. *Korean J Pediatr*. (2018) 61:135–49. doi: 10.3345/kjp.2018.61.5.135

15. Kim JH. Overview of pediatric obesity: diagnosis, epidemiology, and significance. *J Korean Med Assoc*. (2021) 64:401–9. doi: 10.5124/jkma.2021.64.6.401

16. Yoo EG. Waist-to-height ratio as a screening tool for obesity and cardiometabolic risk. *Korean J Pediatr*. (2016) 59:425–31. doi: 10.3345/kjp.2016.59.11.425

17. Ma X, Chen Q, Pu Y, Guo M, Jiang Z, Huang W, et al. Skipping breakfast is associated with overweight and obesity: A systematic review and meta-analysis. *Obes Res Clin Pract*. (2020) 14:1–8. doi: 10.1016/j.orcp.2019.12.002

18. Kim HM, Kang HJ, Lee DH, Jeong SM, Joh HK. Association between breakfast frequency and metabolic syndrome among young adults in South Korea. *Sci Rep*. (2023) 13:16826. doi: 10.1038/s41598-023-43957-3

19. Sun M, Wang X, Wang L, Hu W, Yang Y, Yao N, et al. The mediating role of dietary inflammatory index in the association between eating breakfast and obesity: A cross-sectional study. *Nutrients*. (2022) 14:4378. doi: 10.3390/nu14204378

20. Thorleifsdottir B, Björnsson JK, Benediktsdottir B, Gislason T, Kristbjarnarson H. Sleep and sleep habits from childhood to young adulthood over a 10-year period. *J Psychosom Res*. (2002) 53:529–37. doi: 10.1016/s0022-3999(02)00444-0

21. Ogata H, Hatamoto Y, Goto Y, Tajiri E, Yoshimura E, Kiyono K, et al. Association between breakfast skipping and postprandial hyperglycaemia after lunch in healthy young individuals. *Br J Nutr*. (2019) 122:431–40. doi: 10.1017/s0007114519001235

22. Lee S, Lee DC, Lee HJ. Association between breakfast frequency and insulin resistance in Korean adults with prediabetes: A nationwide population-based cross-sectional study. *Diabetes Metab Syndr*. (2023) 17:102763. doi: 10.1016/j.dsx.2023.102763

23. Kral TV, Whiteford LM, Heo M, Faith MS. Effects of eating breakfast compared with skipping breakfast on ratings of appetite and intake at subsequent meals in 8- to 10-y-old children. *Am J Clin Nutr*. (2011) 93:284–91. doi: 10.3945/ajcn.110.000505

24. Gwin JA, Leidy HJ. Breakfast consumption augments appetite, eating behavior, and exploratory markers of sleep quality compared with skipping breakfast in healthy young adults. *Curr Dev Nutr*. (2018) 2:nzy074. doi: 10.1093/cdn/nzy074

25. Arnotti K, Bamber M. Fruit and vegetable consumption in overweight or obese individuals: A meta-analysis. *West J Nurs Res*. (2020) 42:306–14. doi: 10.1177/0193945919858699

26. Aune D, Giovannucci E, Boffetta P, Fadnes LT, Keum N, Norat T, et al. Fruit and vegetable intake and the risk of cardiovascular disease, total cancer and all-cause mortality-a systematic review and dose-response meta-analysis of prospective studies. *Int J Epidemiol*. (2017) 46:1029–56. doi: 10.1093/ije/dyw319

27. Anggraeni AS, Sukartini T, Kristiawati K. Consumption of fruit and vegetable with risk of obesity in school-age children. *Jurnal Ners*. (2010) 12:27–32. doi: 10.20473/jn.v12i1.3448

28. Nour M, Lutze SA, Grech A, Allman-Farinelli M. The relationship between vegetable intake and weight outcomes: A systematic review of cohort studies. *Nutrients*. (2018) 10:1626. doi: 10.3390/nu10111626

29. Hervik AK, Svihus B. The role of fiber in energy balance. *J Nutr Metab*. (2019) 2019:4983657. doi: 10.1155/2019/4983657

30. Hwang J-Y, Kim Y, Lee HS, Park E, Kim J, Shin S, et al. The development of resources for the application of 2020 Dietary Reference Intakes for Koreans. *J Nutr Health*. (2022) 55:21–35. doi: 10.4163/jnh.2022.55.1.21

31. Jakobsen DD, Brader L, Bruun JM. Association between food, beverages and overweight/obesity in children and adolescents-A systematic review and meta-analysis of observational studies. *Nutrients*. (2023) 15:764. doi: 10.3390/nu15030764

32. Lavelle HV, Mackay DF, Pell JP. Systematic review and meta-analysis of school-based interventions to reduce body mass index. *J Public Health (Oxf)*. (2012) 34:360–9. doi: 10.1093/pubmed/fdr116

33. Krystia O, Ambrose T, Darlington G, Ma DWL, Buchholz AC, Haines J. A randomized home-based childhood obesity prevention pilot intervention has favourable effects on parental body composition: preliminary evidence from the Guelph Family Health Study. *BMC Obes*. (2019) 6:10. doi: 10.1186/s40608-019-0231-y

34. Gato-Moreno M, Martos-Lirio MF, Leiva-Gea I, Bernal-López MR, Vegas-Toro F, Fernández-Tenreiro MC, et al. Early nutritional education in the prevention of childhood obesity. *Int J Environ Res Public Health*. (2021) 18:6569. doi: 10.3390/ijerph18126569

35. Lee JH, Lee HS, Kim H, Kwon YJ, Shin J, Lee JW. Association between nutrition education, dietary habits, and body image misperception in adolescents. *Asia Pac J Clin Nutr*. (2021) 30:512–21. doi: 10.6133/apjcn.202109_30(3).0018

36. Susie Lee D, Semenchenko H. Father absence and pubertal timing in Korean boys and girls. *Evol Med Public Health*. (2023) 11:174–84. doi: 10.1093/emph/eoad010

37. Jasik CB, Lustig RH. Adolescent obesity and puberty: the "perfect storm. *Ann N Y Acad Sci*. (2008) 1135:265–79. doi: 10.1196/annals.1429.009

38. Cardel M, Dulin-Keita A, Casazza K. Contributors to Pediatric Obesity in Adolescence: More than just Energy Imbalance. *Open Obes J*. (2011) 3:17–26. doi: 10.2174/1876823701103010017

39. Im Y, Oh W-O, Suk MH. Adolescent health behaviors according to body mass index. *Child Health Nurs Res*. (2017) 23:1–9. doi: 10.4094/chnr.2017.23.1.1

40. Lee J, Yi K. An analysis of the determinants of adolescents' health inequality in Korea: A view from the students' self-rated health condition and obesity. *Korea Educ Rev*. (2015) 21:217–43.

41. Shah B, Cost KT, Fuller A, Birken CS, Anderson LN. Sex and gender differences in childhood obesity: contributing to the research agenda. *BMJ Nutrition Prev Health*. (2020) 3:387–90. doi: 10.1136/bmjnph-2020-000074

42. Wang VH, Min J, Xue H, Du S, Xu F, Wang H, et al. What factors may contribute to sex differences in childhood obesity prevalence in China? *Public Health Nutr*. (2018) 21:2056–64. doi: 10.1017/s1368980018000290

43. Wouters EJ, Larsen JK, Kremers SP, Dagnelie PC, Geenen R. Peer influence on snacking behavior in adolescence. *Appetite*. (2010) 55:11–7. doi: 10.1016/j.appet.2010.03.002

44. Bauer KW, Larson NI, Nelson MC, Story M, Neumark-Sztainer D. Socio-environmental, personal and behavioural predictors of fast-food intake among adolescents. *Public Health Nutr*. (2009) 12:1767–74. doi: 10.1017/s1368980008004394

45. Keller KL, Kling SMR, Fuchs B, Pearce AL, Reigh NA, Masterson T, et al. A biopsychosocial model of sex differences in children's eating behaviors. *Nutrients*. (2019) 11:682. doi: 10.3390/nu11030682

46. Choi JE, Lee HA, Park SW, Lee JW, Lee JH, Park H, et al. Increase of prevalence of obesity and metabolic syndrome in children and adolescents in Korea during the COVID-19 pandemic: A cross-sectional study using the KNHANES. *Children (Basel)*. (2023) 10:1105. doi: 10.3390/children10071105

47. Yang HJ, Park S, Yoon TY, Ryoo JH, Park SK, Jung JY, et al. Nationwide changes in physical activity, nutrient intake, and obesity in South Korea during the COVID-19 pandemic era. *Front Endocrinol (Lausanne)*. (2022) 13:965842. doi: 10.3389/fendo.2022.965842

48. Oh K, Park S, Park S, Yun S, Choi H, Jeong EK. Changes in food and nutrient intakes in Korean adults before and during the COVID-19 pandemic: data from the 2011-2020 Korea National Health and Nutrition Examination Survey. *Epidemiol Health*. (2023) 45:e2023015. doi: 10.4178/epih.e2023015

49. Kim SY, Yoo DM, Min C, Choi HG. Changes in dietary habits and exercise pattern of Korean adolescents from prior to during the COVID-19 pandemic. *Nutrients*. (2021) 13:3314. doi: 10.3390/nu13103314

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Smartphone three-dimensional imaging for body composition assessment using non-rigid avatar reconstruction

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Background: Modern digital anthropometry applications utilize smartphone cameras to rapidly construct three-dimensional humanoid avatars, quantify relevant anthropometric variables, and estimate body composition.

Methods: In the present study, 131 participants ([73 M, 58 F] age 33.7 ± 16.0 y; BMI 27.3 ± 5.9 kg/m^2, body fat 29.9 ± 9.9%) had their body composition assessed using dual-energy X-ray absorptiometry (DXA) and a smartphone 3D scanning application using non-rigid avatar reconstruction. The performance of two new body fat % estimation equations was evaluated through reliability and validity statistics, Bland–Altman analysis, and equivalence testing.

Results: In the reliability analysis, the technical error of the measurement and intraclass correlation coefficient were 0.5–0.7% and 0.996–0.997, respectively. Both estimation equations demonstrated statistical equivalence with DXA based on ±2% equivalence regions and strong linear relationships (Pearson's *r* 0.90; concordance correlation coefficient 0.89–0.90). Across equations, mean absolute error and standard error of the estimate values were ~ 3.5% and ~ 4.2%, respectively. No proportional bias was observed.

Conclusion: While continual advances are likely, smartphone-based 3D scanning may now be suitable for implementation for rapid and accessible body measurement in a variety of applications.

KEYWORDS

3D scanning, body fat, smartphone, optical imaging, digital anthropometry

1 Introduction

Recent advances in digital anthropometry have highlighted the use of smartphone cameras to obtain visual information that can be used to produce 3-dimensional (3D) humanoid avatars. Several reports have supported the reliability of anthropometric and body composition parameters estimated by such procedures (1–4). While mobile digital anthropometry applications have typically constructed rigid humanoid avatars using two photographic images of static subjects—either from anterior and lateral (2–7) or anterior and posterior views (6, 8)—we recently reported the high reliability of new methods capturing serial images (~150)

during complete rotation of subjects in front of a smartphone camera, followed by non-rigid avatar reconstruction (7). Specifically, the observed technical error of measurement (TEM) across common body circumferences averaged 0.5 cm or 0.9%, slightly lower than errors observed for two large, non-portable 3-dimensional scanning measurement booths that employ rigid avatar reconstruction and are commonly used in research and practice (TEMs of 0.6–0.8 cm or 1.1—1.5%). The combination of greater quantities of visual data and improved data processing pipelines may have contributed to these low errors.

In addition to establishing the reliability of body circumferences from smartphone 3D scanning, considering the validity of subsequent body composition estimation from humanoid avatars is warranted based on the importance of body composition in health, disease, and athletic settings (9–11). Trials to date have evaluated the validity of mobile applications estimating body composition variables from rigid avatars arising from two photographic images, with mixed results (2–6). These methods involve the assessment of a rigid, non-moving human body, which leads to relatively simple avatar reconstruction. Non-smartphone methods, such as traditional scanning booths or sensors positioned in front of turntables, have also employed rigid avatar reconstruction due to the lack of body movement during assessments. In contrast, emerging smartphone methods require participants to complete 360° of rotation in place by taking small, rocking steps while attempting to maintain an A-pose (i.e., standing upright with feet apart and legs straightened, arms straightened and lifted away from the sides of the body). Due to complex body motions generated during this rotation and the resultant body deformations, the 3D avatar must be produced using non-rigid reconstruction, potentially introducing additional error. Following both rigid and non-rigid avatar reconstruction, anthropometric variables from the avatars are used to predict body composition. However, no prior investigations have evaluated the validity of body composition estimates arising from smartphone-based scanning followed by non-rigid avatar reconstruction. Therefore, the purpose of the present study was to examine the validity of body fat percentage (BF%) prediction equations employed by such a smartphone-based 3D scanning application. It was hypothesized that BF% estimates obtained by the smartphone would exhibit strong linear relationships and statistical equivalence as compared to dual-energy X-ray absorptiometry (DXA), an accepted laboratory method of body composition assessment.

2 Method

2.1 Overview

Across two laboratories, adult participants were assessed using a smartphone 3D scanning application and dual-energy X-ray absorptiometry (DXA) at a single research visit. Serial images were collected by the smartphone 3D scanning application during a subject's complete rotation in place, with data subsequently processed using non-rigid avatar reconstruction. The reliability of BF% from duplicate 3D scans was examined, and the validity of BF% values obtained by the 3D scanning application was established through comparison with DXA values.

2.2 Participants

Generally healthy adults (≥18 years of age) were recruited for participation in Lubbock, TX, USA and Baton Rouge, LA, USA. Prospective participants were ineligible if they had a diagnosis of a disease or any medical condition that is known to influence body composition (e.g., Cushing's Syndrome, cancer, type 2 diabetes, chronic kidney disease, and heart failure), a history of major body altering surgery, implanted electrical devices, or were currently pregnant or breastfeeding. All participants provided written informed consent prior to participation, and this study was approved by the Texas Tech University Institutional Review Board (IRB2022-610; date of first approval: 07/23/2022) and the Pennington Biomedical Research Center Institutional Review Board (IRB 2022–002; date of first approval: 2/26/2022). All research was performed in accordance with relevant guidelines and regulations, including the Declaration of Helsinki.

2.3 Laboratory visit

Participants reported to the research laboratory at Texas Tech University (Lubbock, TX, USA) or Pennington Biomedical Research Center (Baton Rouge, LA, USA) after an overnight (≥8 h) period of fasting from foods, fluids, and other substances, and a ≥24-h abstention from exercise and other moderate- or vigorous-intensity physical activity. For assessments, each participant wore minimal form-fitting clothing.

2.4 Smartphone 3D scanning application

The smartphone 3D scanning application required participants to rotate in place on the laboratory flooring, using their own feet to perform the rotation and maintaining an A-pose, approximately 1.7 meters in front of a smartphone. During the rotation, multiple images were captured by the smartphone's built-in camera. Scans were performed using an iPhone 13 Pro Max (model number MLKR3LL/A) with iOS v. 16.5 (Apple, Cupertino, CA, USA) or an iPhone 14 Pro (model number MQ2T3LL/A) with iOS v. 16.6. Each phone was mounted on a tripod for image acquisition. Each scan was automatically processed using the procedures of the manufacturer (Prism Labs, Los Angeles, CA, USA), which include machine learning for data pre-processing through binary segmentation and obtaining frame-to-frame correspondences (7). Humanoid avatars were produced by fully non-rigid reconstruction, and a parameterized body model was fitted to each avatar to normalize the avatar's pose to a canonical pose and promote consistent measurement locations (1). Three scans were performed for each participant, and one scan was randomly selected for each participant, such that the present analysis is based on a single scan per participant to mimic typical use. For these scans, two proprietary BF% algorithms developed by the manufacturer were used: COmpound Circumferences Only (COCO) and Automatic Detection of Athlete Mode (ADAM). The COCO equation employs measurement ratios, such as waist:height, to estimate BF% using coefficients derived from linear regression on the manufacturer's proprietary training data. The ADAM equation computes a weighted average between the COCO BF% and a variant of the Navy method designed to target individuals with lower BF%.

2.5 Dual-energy X-ray absorptiometry

A DXA scan was performed for each participant using a scanner that was calibrated daily according to manufacturer procedures (iDXA, General Electric, Boston, MA, USA with enCORE software versions 13.60.033 and 16.10.151, 16 [SP 1]). For each scan, the participant was positioned supine on the DXA table with hands neutral at their sides and feet together. Consistent positioning of hands and feet was achieved using foam blocks and straps. The region BF% values for the entire body were used in the present analysis.

2.6 Statistical analysis

The reliability of the ADAM and COCO 3D scanning equations was determined by calculating the TEM (i.e., precision error), least significant change (i.e., 2.77 × TEM), and the intraclass correlation coefficient (model 2.1) from duplicate scans, using previously described procedures (12, 13).

The validity of the ADAM and COCO 3D scanning equations were compared to reference DXA values. The linear relationships between 3DO and criterion estimates were established using ordinary least squares regression, with DXA specified as the *x* variable and the 3D scanning equation specified as the *y* variable. To determine if 3DO values demonstrated group-level statistical equivalence with DXA values, equivalence testing (14) was performed using equivalence regions of ±2.0% for BF%, as in a prior investigation (15). The mean difference (i.e., constant error) was calculated, along with the standard error of the estimate (SEE), root mean square error (RMSE), mean absolute error (MAE), Pearson's *r* and R^2, and Lin's concordance correlation coefficient (CCC). Bland–Altman analysis was performed to establish the 95% limits of agreement, alongside linear regression to check for proportional bias (16). Statistical significance was accepted at $p < 0.05$. All statistical analyses were conducted in R (version 4.3.1) (17).

3 Results

3.1 Participants

One hundred and thirty-one participants (73 M, 58 F) with at least one valid scan were included in the validity analysis (Table 1), and a subset of 121 participants with two valid scans were included in the reliability analysis due to the need for duplicate scans to assess reliability. Sample avatars in differing body mass index categories are displayed in Figure 1. Based on self-report, 86 participants were non-Hispanic Caucasian, 21 were Hispanic Caucasian, 13 were Black or African American, 8 were Asian, 2 were Native American or Alaskan, and 1 was Native Hawaiian or other Pacific Islander.

3.2 Reliability

For BF% from the ADAM equation, the TEM, least significant change, and ICC were 0.66%, 1.82%, and 0.996 (95% CI: 0.994–0.997), respectively. For BF% from the COCO equation, the TEM, least significant change, and ICC were 0.50%, 1.39%, and 0.997 (95% CI: 0.996–0.998).

3.3 Validity

Based on the prespecified equivalence regions of ±2.0%, both 3DO BF% equations (ADAM and COCO) demonstrated statistical equivalence DXA BF% (Table 2). Both equations also demonstrated strong, significant correlations with DXA (r 0.90; CCC 0.89–0.90; Figures 2A,C). MAE and RMSE values were 3.4–3.5 and 4.5%, respectively. From Bland–Altman analysis, no proportional bias was observed for either equation (ADAM equation: slope −0.01, 95% CI −0.09, –0.07, Figure 2B; COCO equation: slope −0.07, 95% CI −0.15, 0.01, Figure 2D). Limits of agreement ranged from 8.6 to 8.8%.

4 Discussion

Smartphone-based 3D scanning increases the accessibility of digital anthropometry and body composition estimation. While such mobile scanning methods have typically relied on the generation of rigid avatars from two photographic images, new methods employ the acquisition of numerous images to capture more body shape data for use in non-rigid avatar reconstruction. With recent data indicating the precision of anthropometric and body composition estimates from this method compares favorably to traditional, non-portable 3D scanners (7), a consideration of the validity of resultant body composition estimates was warranted. In the present analysis, we found that two prediction equations demonstrated high reliability and generally strong agreement with DXA for estimation of BF%.

For both BF% equations, very high reliability was observed, with TEM values of 0.50–0.66% from duplicate assessments. Corresponding least significant change values, reflecting the degree of change that would be considered statistically significant, were 1.39–1.82%. Additionally, strong group-level agreement was observed, as supported by statistical equivalence with DXA and strong linear relationships (*r* 0.90; CCC 0.89–0.90). Several additional metrics (SEE, RMSE, and MAE) described the typical individual errors of the equations, with values ranging from 3.4 to 4.5% across metrics and equations. Bland–Altman analysis did not indicate proportional bias in either equation, which is an encouraging indicator due to the common occurrence of large negative proportional bias when applying body composition prediction equations, particularly in consumer-facing assessment methods (15, 18). For example, we previously found notable proportional bias, with slopes of −0.27 to −0.35, when evaluating anthropometric BF% prediction equations developed using the NHANES dataset (15). Additionally, in an evaluation of numerous consumer-grade bioimpedance scales, we found that approximately half exhibited notable proportional bias for BF%, with slopes as large as −0.50 (18). Despite the minimal proportional bias in the present study, the limits of agreement were approximately ±8.6% for both equations, indicating a relatively wide range of individual-level differences between DXA and the prediction equations are possible. However, typical errors—as indicated by the SEE—may be closer to ≤ ±4% in two-thirds of cases. Collectively, these results support high reliability and group-level performance of the prediction equations and provide information regarding the individual-level errors that can be expected with this technology.

A small number of previous investigations have reported the validity of smartphone-based 3D scanning applications, typically using two photographic images, as compared to reference methods (2,

TABLE 1 Participant characteristics.

	All (n = 131)				M (n = 73)				F (n = 58)			
	Mean	SD	Min	Max	Mean	SD	Min	Max	Mean	SD	Min	Max
Age (y)	33.7	16.0	18.0	76.0	36.2	16.8	18.0	76.0	30.5	14.5	18.0	72.0
Height (cm)	172.2	10.0	151.5	194.9	178.4	7.7	163.4	194.9	164.5	6.9	151.5	183.3
Weight (kg)	81.5	21.4	42.0	168.9	90.9	21.3	54.4	168.9	69.8	14.9	42.0	105.4
BMI (kg/m^2)	27.3	5.9	16.9	48.5	28.5	6.0	17.8	48.5	25.8	5.5	16.9	41.9
DXA BF%	29.9	9.9	10.6	54.7	26.7	9.8	10.6	49.4	33.9	8.6	16.9	54.7

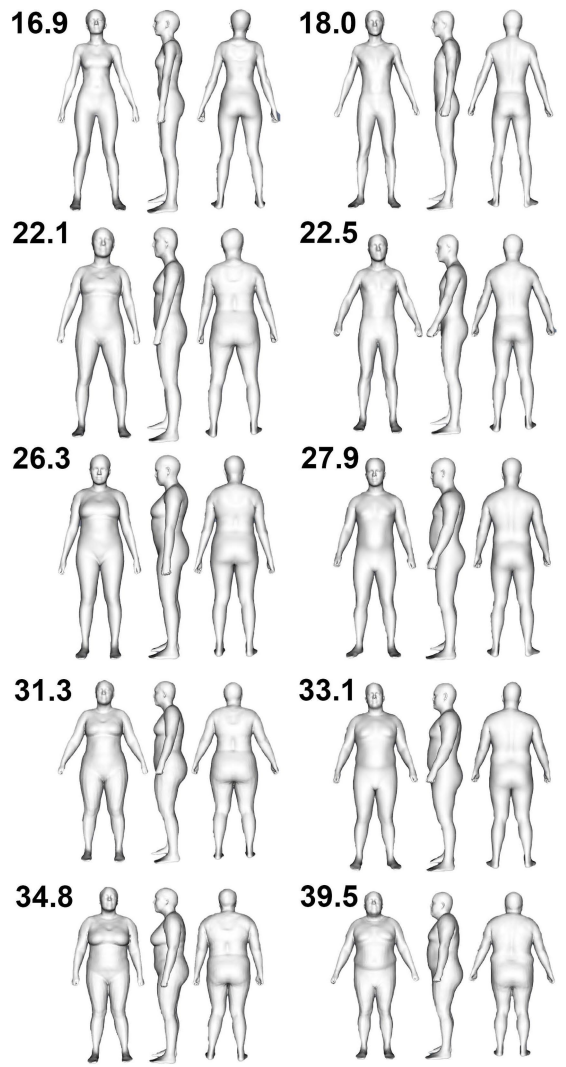

FIGURE 1
Humanoid avatars from 3-dimensional optical imaging scans. Sample female (left column) and male (right column) avatars are displayed for participants categorized as being underweight (i.e., BMI < 18.5 kg/m^2; top row), healthy weight (i.e., 18.5 kg/m^2 < BMI < 24.9 kg/m^2; second row from top), overweight (i.e., 25.0 kg/m^2 < BMI < 29.9 kg/m^2; middle row), or obese (i.e., BMI > 30.0 kg/m^2; bottom two rows).

6, 8). Graybeal et al. (2) demonstrated a similar high reliability of BF% estimates (TEM of 0.3–0.4%) and good group-level performance as compared to a rapid 4-compartment model (r 0.85; statistical equivalence between methods based on a ± 2% equivalence region). However, RMSE values (5.0–5.1%) were slightly higher than in the present investigation (4.5%), and a larger magnitude of proportional bias was observed (slope of −0.25 vs. −0.01 to −0.07 in the present study). In a separate investigation using different 3D scanning applications, Graybeal et al. (6) observed TEM values of 0.3–0.6% for BF%, RMSE values of 3.9–6.2%, and statistical equivalence for some, but not all, scanning applications. As in other studies, negative proportional bias was observed, with slopes of −0.17 to −0.53 across applications. Collectively, some aspects of the performance of the 3D scanning applications evaluated in the present study are similar to prior investigations, with the reduction in the magnitude of proportional bias being a potentially notable difference.

The participants in the present investigation comprised a wide range of adiposity, with DXA BF% values of 10.6–54.7% and BMIs of 16.9–48.5 kg/m^2, as well as expected natural variation in overall body size and shape. An approximately even distribution between sexes (73 M, 58 F) and some representation of racial or ethnic minorities (35% of the sample) were also features of the sample. Collectively, these features contributed to a relatively diverse sample in terms of body size and composition, race and ethnicity, and sex. However, a limitation is the relatively young average age (33.7 ± 16.0 years). As such, the present results provide an important step in evaluating the smartphone-based 3D scanning procedures, but continued investigation is warranted in a variety of groups, including diverse racial and ethnic groups and middle-aged or older adults.

Smartphones are ubiquitous worldwide, with 2022 estimates indicating a median adult smartphone ownership rate of 85% across 18 advanced economies—an increase from 76% in 2018 (19, 20). As such, numerous promising applications of smartphone-based health technologies can be considered. The accessibility of smartphone-based 3D scanning allows for precise anthropometric evaluation and subsequent body composition estimation, providing new opportunities for individual users to track relevant body changes over time. For example, a simple implementation of this technology is the ability for smartphone-based 3D scanning to provide a precise estimate of waist circumference, thereby allowing one important component of cardiometabolic risk (21) to be easily assessed without the need for a trained assessor. Additionally, there are opportunities for anthropometric and body composition estimates to be integrated into weight management mobile applications to provide customized feedback and progress tracking. While the ability of 3D scanning to aid in the success of such weight management programs will be a topic for future investigation, the automated nature of such procedures reduces barriers to physical evaluations as compared to decades past. The ability to rapidly obtain automated measurements at home, using smartphone capabilities, could eliminate the need for in-person anthropometric assessment by health providers. Beyond

TABLE 2 Validity results.

DXA				3D scanning					Validity analysis						
Mean	SD	Min	Max	BF% estimate	Mean	SD	Min	Max	MD	SD of MD	SEE	RMSE	*r*	CCC	Equivalence?
29.9	9.9	10.6	54.7	ADAM	29.7	9.8	11.0	55.6	−0.2	4.5	4.3	4.5	0.90*	0.90*	Y ($p < 0.01$)
				COCO	31.1	9.3	14.4	56.0	1.3	4.4	4.1	4.5	0.90*	0.89*	Y ($p = 0.03$)

MD, mean difference; SEE, standard error of the estimate; RMSE, root mean square error; r, Pearson's correlation coefficient; CCC, Lin's concordance correlation coefficient; Y, yes (statistically equivalent); BF%, body fat %; ADAM, Automatic Detection of Athlete Mode 3D scanning equation; COCO, COmpound Circumferences Only 3D scanning equation.
*$p < 0.001$.

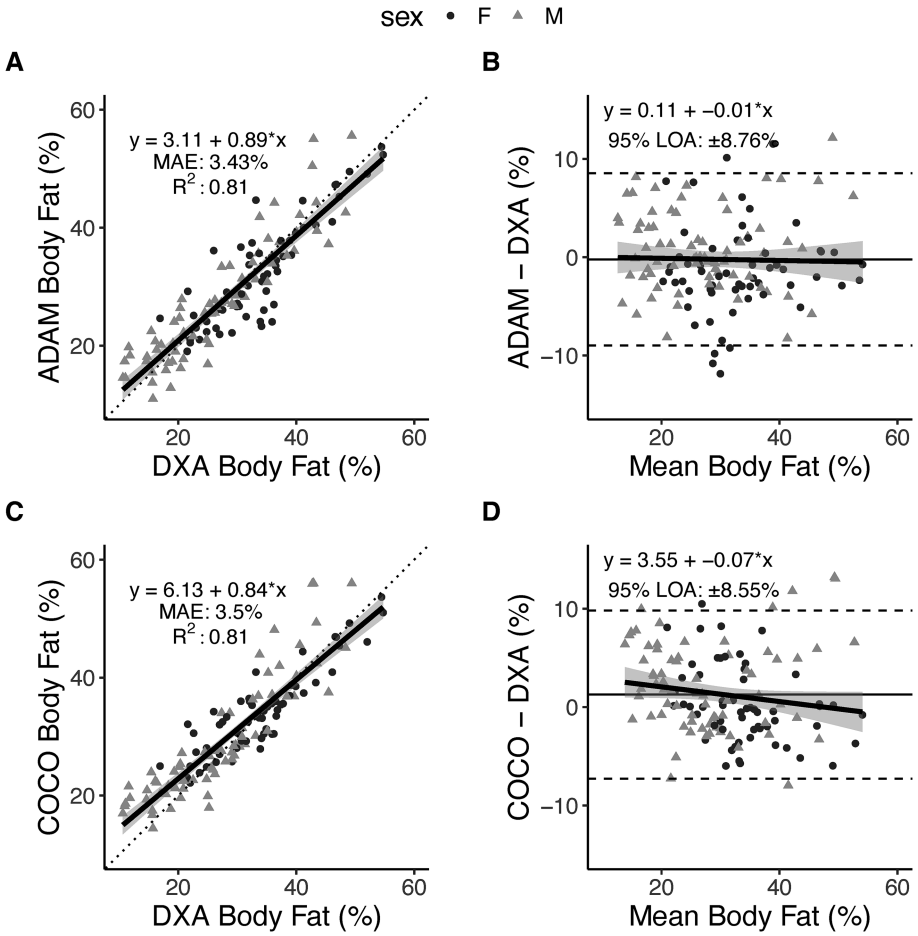

FIGURE 2
Body fat percentage estimates from smartphone-based 3-dimensional optical imaging. Two prediction equations, ADAM and COCO, were evaluated as compared to DXA. Relationships between 3DO-based values and DXA values are displayed in panels **(A,C)**, with the dotted line indicating the perfect linear relationship (line of identity) and the solid black line with shading representing the observed linear relationship and 95% confidence bands. Data points indicate individual participants. Bland–Altman plots are displayed in panels **(B,D)**, with dashed lines indicated the 95% limits of agreement, the horizontal solid black line indicating the mean difference (i.e., constant error), and the diagonal black line with shading indicating the observed linear relationship and 95% confidence bands.

using simple metrics like waist circumference and BF%, there are also opportunities to employ various machine learning and artificial intelligence procedures to characterize unique body phenotypes and their relationship to health and disease parameters (22, 23). Pairing smartphone-based 3D scans with relevant clinical data—such as blood lipids, glucose, and blood pressure—may allow for better understanding of the influence of body shape and size on relevant cardiometabolic risk factors, both at the group and individual level. Future investigations including a greater proportion of participants with obesity and related comorbidities will provide further clarity regarding the utility of this technology. Due to the lack of risk and non-invasive nature of 3D scanning assessments, other medical applications—such as the monitoring of pregnant and breastfeeding individuals—should also be considered in subsequent work. While

future research and development will be needed to realize the potential of 3D scanning as a component of health assessment, emerging findings indicate notable potential of smartphone-based methods.

In summary, the present study demonstrates the validity of body composition estimation from smartphone-based 3D scanning. Unlike previous trials of smartphone technologies, the humanoid avatars constructed by the 3D scanning application were based on large amounts of visual data collected during complete subject rotation. With the reliability (7) and validity of these procedures established, new applications of this technology can be investigated. Additionally, continued refinement of body composition prediction in diverse populations can promote the lowest errors achievable and maximize the ability to accurately track changes over time. While continual advances are likely, smartphone-based 3D scanning may now be suitable for implementation for rapid and accessible body measurement in a variety of applications.

Data availability statement

The datasets presented in this article are not readily available because institutional approval is required. Requests to access the datasets should be directed to grant.tinsley@ttu.edu.

Ethics statement

The studies involving humans were approved by the Texas Tech University Institutional Review Board and Pennington Biomedical Research Center Institutional Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

GT: Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. CR: Writing – review & editing, Project administration, Methodology, Investigation, Data curation. CF: Writing – review & editing, Project administration, Methodology, Investigation, Data curation. MS: Writing – review & editing, Project administration, Methodology, Investigation, Data curation. ET: Writing – review & editing, Project administration, Investigation, Data curation. CM: Writing – review & editing, Project administration, Investigation, Data curation. SH: Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Data curation, Conceptualization.

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Conflict of interest

GMT has received in-kind support for his research laboratory, in the form of equipment loan or donation, from manufacturers of body composition assessment devices, including Size Stream LLC; Naked Labs Inc.; Prism Labs Inc.; RJL Systems; MuscleSound; and Biospace, Inc. (DBA InBody). None of these entities played any role in the present investigation, beyond the role of Prism Labs described in the Funding Statement. SBH reports personal fees from Medifast Corporation, Tanita Corporation, Novo Nordisk, Amgen, Versanis, and Novartis, outside the submitted work.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Tinsley GM, Harty PS, Siedler MR, Stratton MT, Rodriguez C. Improved precision of 3-dimensional optical imaging for anthropometric measurement using non-rigid avatar reconstruction and parameterized body model fitting. *Clin Nutr Open Sci*. (2023) 50:40–5. doi: 10.1016/j.nutos.2023.07.002

2. Graybeal AJ, Brandner CF, Tinsley GM. Validity and reliability of a mobile digital imaging analysis trained by a four-compartment model. *J Hum Nutr Diet*. (2023) 36:905–11. doi: 10.1111/jhn.13113

3. Graybeal AJ, Brandner CF, Tinsley GM. Evaluation of automated anthropometrics produced by smartphone-based machine learning: a comparison with traditional anthropometric assessments. *Br J Nutr*. (2023) 130:1077–87. doi: 10.1017/s0007114523000090

4. Smith B, McCarthy C, Dechenaud ME, Wong MC, Shepherd J, Heymsfield SB. Anthropometric evaluation of a 3d scanning mobile application. *Obesity*. (2022) 30:1181–8. doi: 10.1002/oby.23434

5. Graybeal AJ, Brandner CF, Compton AT, Swafford SH, Henderson A, Aultman R, et al. Smartphone derived anthropometrics: agreement between a commercially available smartphone application and its parent application intended for use at point-of-care. *Clin Nutr ESPEN*. (2024) 59:107–12. doi: 10.1016/j.clnesp.2023.11.021

6. Graybeal AJ, Brandner CF, Tinsley GM. Visual body composition assessment methods: a 4-compartment model comparison of smartphone-based artificial intelligence for body composition estimation in healthy adults. *Clin Nutr*. (2022) 41:2464–72. doi: 10.1016/j.clnu.2022.09.014

7. Tinsley GM, Rodriguez C, Siedler MR, Tinoco E, White SJ, LaValle C, et al. Mobile phone applications for 3-dimensional scanning and digital anthropometry: a precision comparison with traditional scanners. *Eur J Clin Nutr*. (2024) 78:509–14. doi: 10.1038/s41430-024-01424-w

8. Majmudar MD, Chandra S, Yakkala K, Kennedy S, Agrawal A, Sippel M, et al. Smartphone camera based assessment of adiposity: a validation study. *NPJ Digit Med*. (2022) 5:79. doi: 10.1038/s41746-022-00628-3

9. Glaser Y, Shepherd J, Leong L, Wolfgruber T, Lui L-Y, Sadowski P, et al. Deep learning predicts all-cause mortality from longitudinal total-body Dxa imaging. *Commun Med*. (2022) 2:102. doi: 10.1038/s43856-022-00166-9

10. Gupta P, Lanca C, Gan ATL, Soh P, Thakur S, Tao Y, et al. The association between body composition using dual energy X-ray absorptiometry and type-2 diabetes: a systematic review and meta-analysis of observational studies. *Sci Rep*. (2019) 9:12634. doi: 10.1038/s41598-019-49162-5

11. Ackland TR, Lohman TG, Sundgot-Borgen J, Maughan RJ, Meyer NL, Stewart AD, et al. Current status of body composition assessment in sport: review and position statement on behalf of the ad hoc research working group on body composition health and performance, under the auspices of the I.O.C. Medical commission. *Sports Med*. (2012) 42:227–49. doi: 10.2165/11597140-000000000-00000

12. Shrout PE, Fleiss JL. Intraclass correlations: uses in assessing rater reliability. *Psychol Bull*. (1979) 86:420–8. doi: 10.1037/0033-2909.86.2.420

13. Glüer CC, Blake G, Lu Y, Blunt BA, Jergas M, Genant HK. Accurate assessment of precision errors: how to measure the reproducibility of bone densitometry techniques. *Osteoporos Int*. (1995) 5:262–70. doi: 10.1007/bf01774016

14. Dixon PM, Saint-Maurice PF, Kim Y, Hibbing P, Bai Y, Welk GJ. A primer on the use of equivalence testing for evaluating measurement agreement. *Med Sci Sports Exerc*. (2018) 50:837–45. doi: 10.1249/mss.0000000000001481

15. Tinsley GM. Five-component model validation of reference, laboratory and field methods of body composition assessment. *Br J Nutr*. (2021) 125:1246–59. doi: 10.1017/S0007114520003578

16. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet*. (1986) 1:307–10. doi: 10.1016/S0140-6736(86)90837-8

17. R Core Team. R: a language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing (2023).

18. Siedler MR, Rodriguez C, Stratton MT, Harty PS, Keith DS, Green JJ, et al. Assessing the reliability and cross-sectional and longitudinal validity of fifteen bioelectrical impedance analysis devices. *Br J Nutr*. (2023) 130:827–40. doi: 10.1017/s0007114522003749

19. Center PR. 3. Internet, smartphone and social media use. Washington, D.C., USA: Pew Research Center's Global Attitudes Project (2023).

20. Silver L. Smartphone ownership is growing rapidly around the world, but not always equally. Washington, D.C., USA: Pew Research Center's Global Attitudes Project (2020).

21. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: a joint interim statement of the international diabetes federation task force on epidemiology and prevention; National Heart, Lung, and Blood Institute; American Heart Association; world heart federation; international atherosclerosis society; and International Association for the Study of obesity. *Circulation*. (2009) 120:1640–5. doi: 10.1161/circulationaha.109.192644

22. Bennett JP, Liu YE, Quon BK, Kelly NN, Leong LT, Wong MC, et al. Three-dimensional optical body shape and features improve prediction of metabolic disease risk in a diverse sample of adults. *Obesity*. (2022) 30:1589–98. doi: 10.1002/oby.23470

23. Ng BK, Sommer MJ, Wong MC, Pagano I, Nie Y, Fan B, et al. Detailed 3-dimensional body shape features predict body composition, blood metabolites, and functional strength: the shape up! Studies. *Am J Clin Nutr*. (2019) 110:1316–26. doi: 10.1093/ajcn/nqz218

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Correlation between body mass index and gender-specific 28-day mortality in patients with sepsis: a retrospective cohort study

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Objective: To investigate the potential correlation between body mass index (BMI) and the 28-day mortality rate among sepsis patients and the gender difference in this association.

Design: The current research was a retrospective cohort study.

Participants: A total of 14,883 male and female cohorts of sepsis patients were included in the Medical Information Mart for Intensive Care IV (MIMIC-IV V2.2) database. Patients in each gender cohort were further classified as underweight, normal weight, overweight, or obese according to BMI and the World Health Organization (WHO) BMI categories.

Outcomes: The 28-day mortality from the date of ICU hospitalization was the primary outcome measure.

Results: The BMI and 28-day mortality exhibited an L-shaped relationship (p for nonlinearity <0.001) with significant gender-specific differences. Subgroup analysis revealed different association patterns between the male and female cohorts. Specifically, BMI and mortality exhibited a U-shaped curve relationship among the males (p for nonlinearity <0.001) and an L-shaped relationship among the females (p for nonlinearity = 0.045).

Conclusion: This study proposes a link between extreme BMI and 28-day mortality in patients with sepsis. Underweight patients have an increased risk of mortality; however, this risk decreases in overweight and obese patients. Upon stratifying by sex, a U-shaped pattern was observed, indicating an association between BMI and 28-day mortality in males, while an L-shaped pattern emerged in females.

KEYWORDS

sepsis, obesity, mortality, body mass index, gender

Introduction

In the last 3 years, there has been a significant rise in the worldwide occurrence of overweight and obese individuals. The overall incidence has risen from 28.8 to 36.9% among males, and among women, it has increased from 29.8 to 38.0% (1). Obesity traits are linked to the leading global causes of death (2), with discernible gender differences in the risk impact

of certain diseases. For instance, research indicates that overweight women have a higher risk of type 2 diabetes than men. In comparison, overweight men have a higher risk of chronic diseases like chronic kidney disease and chronic obstructive pulmonary disease (COPD) (3).

The yearly global incidence of sepsis is approximately 30 million, resulting in 6 million deaths (4). However, obesity unexpectedly appears to protect against death from all causes in individuals with sepsis (5). This was called "reverse epidemiology" or the "obesity paradox" (6, 7). Previous studies found that overweight and obese individuals had much lower mortality rates associated with sepsis than normal-weight individuals (5, 8, 9). Research has provided insights into the link between body mass index (BMI), sepsis-associated death, and age (10); however, a specific gender-based impact of BMI on sepsis-related mortality and the gender-specific link between BMI and sepsis-associated mortality in individuals has not been explicitly addressed.

A critical analysis of existing research reveals methodological and sample characteristic differences, which brings the reliability of these studies to question. To address this knowledge gap, the current study explored the relationship between BMI, gender, and sepsis mortality, overcoming previously identified limitations. This offers a new insight into the intricate interplay of obesity, gender, and sepsis mortality.

In addition, previous research frequently regards BMI as either a continuous or categorical factor, which fails to fully capture the intricate dose–response correlation between BMI and sepsis-associated mortality. The present research work deviated from traditional methods by utilizing restricted cubic splines (RCSs) to elucidate the dose–response relationship. After comprehensively evaluating for the obesity paradox in a cohort of patients with sepsis, the main objective was to get a detailed comprehension of a possible obesity paradox in sepsis prognosis. Investigate for differences in the association between BMI and mortality in men versus women.

Methods

Study design

The current work adhered to the standards outlined in the STROBE statement. This retrospective investigation of patients with sepsis was longitudinal and single-center.

Patient and public involvement

The study did not include active participation from patients or the general public.

Data source

The Medical Information Mart for Intensive Care IV (MIMIC-IV V2.2) database is a carefully curated and identifiable collection of medical records from patients hospitalized in the intensive care unit (ICU) between 2008 and 2019. The authorization to utilize MIMIC-IV data for research (Certification Number: 38807989) was secured, having satisfactorily concluded the National Institutes of Health Protecting Human Research Participants training course. The Ethics Committee of Kunshan First People's Hospital approved the study (Ethics Number 2023–04-001-K02).

Study population

The study comprised 14,883 individuals diagnosed with sepsis who had BMI information. Participants were recruited from the MIMIC-IV database (11). The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) guidelines were used to describe sepsis. The initial screening included patients with a sepsis diagnosis, including those with sepsis, severe sepsis, and septic shock (ICD9 codes: 99591, 99,592, 78,552, respectively). Exclusion criteria included patients who were under 18 years old and had ICU stays of less than 24 h. For multiple admissions, only the first ICU admission records were considered.

Data retrieval

The extraction of data was executed with Structured Query Language (SQL). Patients' age, sex, race, BMI, and Charlson comorbidity index were recorded. Records about the administration of vasopressors, mechanical ventilation, and sedatives within the first 24 h after admission to the ICU were also collected. Comorbidity data, such as diabetes mellitus, congestive heart failure (CHF), coronary artery disease (CAD), hypertension, stroke, renal disease, atrial fibrillation (AFIB), liver disease, chronic pulmonary disease, and malignant tumor, were gathered using the International Classification of Diseases coding systems. The initial data collected at the onset of sepsis included vital signs (heart rate and minimum arterial pressure), the severity of illness [Simplified Acute Physiologic Score (SAPS), laboratory tests partial pressure of oxygen (PO_2), hemoglobin concentration, white blood cell count, lactate, creatinine, glucose and pH levels] and sequential organ failure assessment (SOFA), were retrieved.

Exposure and outcomes

The exposure was BMI, calculated as weight (kg)/height^2 (m^2). The primary outcome assessed was the mortality due to any cause within 28 days. Secondary outcomes examined were the mortality after 1 year and the duration of stay in the ICU.

Statistical analysis

This retrospective study did not use *a priori* statistical analysis strategy and statistical power calculation. Based on the data that was already present in the database, the sample size was selected. The primary indicator for the research was BMI. All missing values, entries with recording errors, and other potential confounding factors with missing values exceeding 10% were excluded.

Supplementary Table S1 shows the variable missing rates. Missing values for each variable were estimated using multiple imputations (9). Multicollinearity among variables was detected using the variance

inflation factor. The absence of multicollinearity for each variable was indicated by a variance inflation factor of <5 (Supplementary Table S2).

BMI was categorized into underweight (less than 18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), and obese (more than 30 kg/m^2) using the World Health Organization (WHO) standards. Fifteen patients were excluded due to presumed erroneous data defined as BMI > 100 kg/m^2. The patients were also grouped according to age as <60, 60–80, and ⩾ 80. Categorical variables were represented using numbers and percentages, and between-group differences were found using chi-squared and Fisher's exact tests. Continuous variables were expressed using medians and interquartile-range values, and between-group differences were identified using the Mann–Whitney U test. Multivariable logistic regression models were used to evaluate the association between different BMI categories and 28-day mortality in sepsis patients. We constructed two regression models to control for confounding biases by adjusting for covariates. The selection of covariates was driven both theoretically and statistically. Some covariates, theoretically associated with mortality, were fixed in the model, such as age, gender, race, SAPS, SOFA, and Charlson Comorbidity Index. Other variables were selected using statistical methods. First, variables with variance inflation factors greater than 5 were excluded to avoid multicollinearity. We constructed both unadjusted and adjusted models. The adjusted model included age, gender, race, SAPS, SOFA, Charlson comorbidity index, diabetes, hypertension, coronary artery disease, congestive heart failure, atrial fibrillation, malignancy, stroke, chronic obstructive pulmonary disease, renal disease, liver disease and glucose. The nonlinear relationship between BMI and 28-day all-cause mortality was assessed using RCSs Nonlinear model knots were used to distribute BMI into quartiles. The nonlinear association between BMI and patient all-cause mortality was analyzed, and its p-value was calculated.

A subgroup analysis of sex and age was also performed to explore potential relationships within specific subgroups.

The statistical analyses were conducted using R software (version 4.2.3; R Foundation for Statistical Computing, Vienna, Austria) and Empowerstats.[1] Statistical significance was determined at a two-tailed p-value of less than 0.05.

Results

Patient selection

Supplementary Figure S1 outlines the patient selection process identifying 25,599 records. The cohort consisted of 14,883 patients after excluding unqualified records.

Demographic and hospitalization characteristics by BMI

Table 1 summarizes the demographic and hospitalization characteristics of male patients with sepsis (n = 9,022). A significant age difference exists among the BMI categories (p < 0.001). Older age showed a significant association with lower BMI and vice versa. Remarkably, BMI significantly impacts disease severity, as evidenced by SAPS (p < 0.001) and the Charlson comorbidity index (p < 0.001). This demonstrates an inverse relationship between lower BMI and higher scores on SAPS and the Charlson comorbidity index. Significant differences in comorbidities (p < 0.001) were observed, including atrial fibrillation, diabetes, renal disease, COPD, hypertension, liver disease, and metastatic cancer. Key vital signs and laboratory parameters exhibited significant differences among BMI categories. Clinical interventions, such as mechanical ventilation and vasopressor use, displayed BMI-related variations (p < 0.001).

Table 2 presents the demographic and hospitalization characteristics of female patients with sepsis (n = 5,861). Similar to males, older age was significantly associated with lower BMI (p < 0.001). Both SOFA scores (p = 0.047) and the Charlson comorbidity index (p = 0.044) showed significant differences across BMI groups. Although the median Charlson comorbidity index was consistent at 5.0 across BMI groups, further analysis suggested that females with lower BMI tended to have a higher burden of comorbidities, which is reflected in the significant differences observed across the BMI categories. Significant differences in comorbidities (p < 0.001) were observed, including diabetes, renal disease, COPD, and hypertension. BMI-related differences were noted in the vital signs and laboratory parameters. Clinical interventions, such as mechanical ventilation, exhibited BMI-related variations (p < 0.001).

Comparison of outcomes in different genders

Table 3 and Supplementary Table S3 presents the patient outcomes stratified by BMI and age categories. There were significant differences in the duration of ICU stay and the rates of death at 28 days and 1 year among male patients, depending on their BMI categories (p < 0.001), with obese patients having the longest mean ICU stay of 3.4 (1.7, 8.0) days. Underweight male patients experienced the highest 28-day (22%) and 1-year (53.2%) mortality. Obese males had the lowest risk of death, with a 28-day and 1-year mortality of 12.5 and 22.3%, respectively.

In female patients, ICU stay did not differ between BMI groups (p = 0.108). However, 28-day and 1-year mortality varied substantially by BMI (p < 0.001). Underweight females had markedly elevated mortality, with 28-day and 1-year rates of 28.2 and 44.1%, respectively. Obese females experienced relatively lower mortality of 15.7% at 28 days and 28.6% at 1 year.

Gender differences in the correlation between BMI and mortality

Supplementary Table S4 presents the multivariable logistic regression analysis results showing the relationship between mortality and BMI. After accounting for potential confounders that might influence the results (Supplementary Table S5), each unit rise in BMI was linked to 2% lower odds of 28-day mortality [adjusted odds ratio (OR) = 0.98, 95% confidence interval (CI) = 0.98, 0.99, p < 0.001]. When stratified by gender, the outcomes showed a significant correlation (p for

1 http://www.empowerstats.com

TABLE 1 Demographic information and hospitalization characteristics of male sepsis patients.

Demographic or hospitalization characteristic	Overall *n* = 9,022	Healthy weight (18.5–24.9 kg/m^2); *n* = 2,441	Underweight (<18.5 kg/m^2); *n* = 186	Overweight (25.0–29.9 kg/m^2); *n* = 3,276	Obese (≥30.0 kg/m^2); *n* = 3,119	*P*-value
Age (years)	63.6 ± 15.1	65.3 ± 16.8	65.4 ± 17.1	64.7 ± 15.0	61.1 ± 13.4	< 0.001
Age, n (%)						< 0.001
<60	3,207 (35.5)	791 (32.4)	60 (32.3)	1,084 (33.1)	1,272 (40.8)	
60–80	4,442 (49.2)	1,093 (44.8)	80 (43)	1,638 (50)	1,631 (52.3)	
≥80	1,373 (15.2)	557 (22.8)	46 (24.7)	554 (16.9)	216 (6.9)	
Race and ethnicity, n (%)						< 0.001
Asian	239 (2.7)	130 (5.3)	4 (2.2)	76 (2.3)	29 (0.9)	
Black	563 (6.2)	188 (7.7)	28 (15.1)	159 (4.9)	188 (6)	
Hispanic	307 (3.4)	98 (4)	8 (4.3)	105 (3.2)	96 (3.1)	
White	6,191 (68.7)	1,569 (64.3)	109 (58.6)	2,320 (70.9)	2,193 (70.3)	
Unknown/Other	1716 (19.0)	454 (18.6)	37 (19.9)	612 (18.7)	613 (19.7)	
SAPS score	37.0 (29.0, 47.0)	37.0 (30.0, 47.0)	40.0 (32.2, 48.0)	36.0 (29.0, 46.0)	37.0 (29.0, 47.0)	< 0.001
SOFA	2.0 (0.0, 4.0)	2.0 (0.0, 4.0)	1.0 (0.0, 3.0)	2.0 (0.0, 4.0)	2.0 (0.0, 4.0)	0.01
Charlson comorbidity index	5.0 (3.0, 7.0)	5.0 (3.0, 7.0)	6.0 (4.0, 8.0)	4.0 (3.0, 7.0)	4.0 (3.0, 6.0)	< 0.001
Comorbidity						
AFIB, n (%)	3,110 (34.5)	818 (33.5)	46 (24.7)	1,161 (35.4)	1,085 (34.8)	0.016
Diabetes, n (%)	2,847 (31.6)	565 (23.1)	46 (24.7)	922 (28.1)	1,314 (42.1)	< 0.001
CHF, n (%)	1,461 (16.2)	390 (16)	29 (15.6)	513 (15.7)	529 (17)	0.537
Renal disease, n (%)	7,445 (82.5)	1864 (76.4)	143 (76.9)	2,656 (81.1)	2,782 (89.2)	< 0.001
COPD, n (%)						< 0.001
	543 (6.0)	146 (6)	23 (12.4)	165 (5)	209 (6.7)	
Hypertension, n (%)	4,075 (45.2)	933 (38.2)	55 (29.6)	1,550 (47.3)	1,537 (49.3)	< 0.001
CAD, n (%)	1,186 (13.1)	304 (12.5)	20 (10.8)	416 (12.7)	446 (14.3)	0.104
Stroke, n (%)	874 (9.7)	252 (10.3)	16 (8.6)	325 (9.9)	281 (9)	0.359
Liver disease, n (%)	2,123 (23.5)	581 (23.8)	64 (34.4)	706 (21.6)	772 (24.8)	< 0.001

(Continued)

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TABLE 1 (Continued)

Demographic or hospitalization characteristic	Overall $n = 9,022$	Healthy weight (18.5–24.9 kg/m^2); $n = 2,441$	Underweight (<18.5 kg/m^2); $n = 186$	Overweight (25.0–29.9 kg/m^2); $n = 3,276$	Obese (≥30.0 kg/m^2); $n = 3,119$	*P*-value
Metastatic cancer, n (%)	2036 (22.6)	611 (25)	62 (33.3)	794 (24.2)	569 (18.2)	< 0.001
Vital signs						
MAP (mm Hg)	53.7 ± 11.3	53.0 ± 11.5	51.6 ± 12.5	54.4 ± 10.9	53.8 ± 11.5	< 0.001
Heart rate (beats/min)	116.3 ± 24.4	116.7 ± 23.8	121.6 ± 30.8	115.0 ± 24.5	117.1 ± 24.3	< 0.001
Laboratory tests						
PO2 (mmHg)	67.0 (42.0, 95.0)	67.0 (41.0, 104.0)	48.0 (36.0, 90.8)	71.0 (44.0, 99.0)	64.0 (42.0, 87.0)	< 0.001
Lactate (mmol/L)	2.4 (1.7, 3.7)	2.5 (1.7, 3.8)	2.1 (1.6, 3.4)	2.4 (1.8, 3.6)	2.4 (1.7, 3.7)	0.08
Hemoglobin (g/dL)	8.7 ± 1.9	8.5 ± 1.8	8.2 ± 1.8	8.7 ± 1.9	8.9 ± 2.0	< 0.001
pH	7.3 ± 0.1	7.3 ± 0.1	7.3 ± 0.1	7.3 ± 0.1	7.3 ± 0.1	< 0.001
Creatinine (mg/dL)	1.1 (0.9, 1.7)	1.0 (0.8, 1.6)	1.0 (0.8, 2.0)	1.1 (0.9, 1.6)	1.2 (0.9, 1.9)	< 0.001
White blood cell counts (×10^9/L)	16.0 (12.0, 21.2)	15.5 (11.6, 20.6)	16.0 (11.5, 21.5)	15.7 (11.9, 20.5)	16.7 (12.5, 21.9)	< 0.001
Glucose, (mg/dL)	131.0 (108.0, 166.0)	124.0 (103.0, 156.0)	123.0 (103.0, 152.8)	131.0 (108.0, 164.0)	138.0 (112.0, 177.0)	< 0.001
Interventions						
Mechanical ventilation use, n (%)	8,459 (93.8)	2,233 (91.5)	170 (91.4)	3,089 (94.3)	2,967 (95.1)	< 0.001
Vasopressor use, n (%)	5,552 (61.5)	1,464 (60)	100 (53.8)	2038 (62.2)	1950 (62.5)	0.027
Sedative use, n (%)	635 (7.0)	156 (6.4)	8 (4.3)	225 (6.9)	246 (7.9)	0.064

Continuous Variables: Normally distributed variables are shown as mean (± SD), and non-normally distributed variables as median (IQR). Categorical Variables: Categorical variables are presented as counts and percentages (%). BMI, Body Mass Index; MAP, Mean Arterial Pressure; SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment; COPD, Chronic obstructive pulmonary disease; CAD, Coronary artery disease; CHF, Congestive heart failure; AFIB, Atrial fibrillation.

10.3389/fmed.2024.1462637

TABLE 2 Demographic information and hospitalization characteristics of female sepsis patients.

Demographic or hospitalization characteristic	Overall *n* = 5,861	Healthy weight (18.5–24.9 kg/m^2); *n* = 1,767	Underweight (<18.5 kg/m^2); *n* = 245	Overweight (25.0–29.9 kg/m^2); *n* = 1,632	Obese (≥30.0 kg/m^2); *n* = 2,217	*P*-value
Age (years)	66.2 ± 16.0	67.6 ± 17.1	68.9 ± 16.8	67.3 ± 16.5	64.1 ± 14.4	< 0.001
Age, n (%)						< 0.001
<60	1775 (30.3)	511 (28.9)	57 (23.3)	470 (28.8)	737 (33.2)	
60–80	2,771 (47.3)	751 (42.5)	113 (46.1)	726 (44.5)	1,181 (53.3)	
≥80	1,315 (22.4)	505 (28.6)	75 (30.6)	436 (26.7)	299 (13.5)	
Race and ethnicity, n (%)						< 0.001
Asian	124 (2.1)	68 (3.9)	7 (2.9)	35 (2.1)	14 (0.6)	
Black	568 (9.7)	143 (8.1)	25 (10.2)	150 (9.2)	250 (11.3)	
Hispanic	173 (3.0)	33 (1.9)	1 (0.4)	54 (3.3)	85 (3.8)	
White	3,992 (68.2)	1,208 (68.4)	171 (69.8)	1,127 (69.2)	1,486 (67.1)	
Unknown/Other	997 (17.0)	313 (17.7)	41 (16.7)	263 (16.1)	380 (17.2)	
SAPS score	38.0 (30.0, 48.0)	38.0 (30.0, 48.0)	40.0 (31.0, 52.0)	38.0 (30.0, 48.0)	38.0 (30.0, 48.0)	0.135
SOFA	1.0 (0.0, 3.0)	1.0 (0.0, 3.0)	1.0 (0.0, 3.0)	1.0 (0.0, 3.0)	1.0 (0.0, 4.0)	0.047
Charlson comorbidity index	5.0 (3.0, 7.0)	5.0 (3.0, 7.0)	5.0 (4.0, 7.0)	5.0 (3.0, 7.0)	5.0 (3.0, 7.0)	0.044
Comorbidity						
AFIB, n (%)	1890 (32.2)	588 (33.3)	69 (28.2)	530 (32.5)	703 (31.7)	0.382
Diabetes, n (%)	1739 (29.7)	341 (19.3)	32 (13.1)	443 (27.1)	923 (41.6)	< 0.001
CHF, n (%)	1,085 (18.5)	331 (18.7)	36 (14.7)	321 (19.7)	397 (17.9)	0.22
Renal disease, n (%)	4,748 (81.0)	1,294 (73.2)	171 (69.8)	1,293 (79.2)	1990 (89.8)	< 0.001
COPD, n (%)	491 (8.4)	137 (7.8)	30 (12.2)	118 (7.2)	206 (9.3)	0.012
Hypertension, n (%)	2,672 (45.6)	728 (41.2)	90 (36.7)	761 (46.6)	1,093 (49.3)	< 0.001
CAD, n (%)	482 (8.2)	132 (7.5)	16 (6.5)	134 (8.2)	200 (9)	0.248
Stroke, n (%)	668 (11.4)	224 (12.7)	26 (10.6)	193 (11.8)	225 (10.1)	0.081
Liver disease, n (%)	1,302 (22.2)	370 (20.9)	62 (25.3)	364 (22.3)	506 (22.8)	0.321
Metastatic cancer, n (%)	1,382 (23.6)	475 (26.9)	76 (31)	357 (21.9)	474 (21.4)	< 0.001

(Continued)

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TABLE 2 (Continued)

Demographic or hospitalization characteristic	Overall $n = 5,861$	Healthy weight (18.5–24.9 kg/m^2); $n = 1,767$	Underweight (<18.5 kg/m^2); $n = 245$	Overweight (25.0–29.9 kg/m^2); $n = 1,632$	Obese (≥30.0 kg/m^2); $n = 2,217$	*P*-value
Vital signs						
MAP (mm Hg)	51.3 ± 11.0	51.7 ± 11.3	51.2 ± 11.7	51.3 ± 10.9	50.9 ± 10.9	0.132
Heart rate (beats/min)	118.7 ± 24.4	119.6 ± 24.6	120.5 ± 24.4	117.5 ± 24.3	118.6 ± 24.2	0.044
Laboratory tests						
PO2 (mmHg)	62.0 (39.0, 90.0)	63.0 (40.0, 94.0)	51.5 (36.8, 86.5)	64.0 (39.0, 92.0)	61.0 (39.0, 85.0)	0.003
Lactate (mmol/L)	2.5 (1.6, 3.9)	2.4 (1.6, 3.9)	2.1 (1.5, 3.5)	2.5 (1.6, 3.9)	2.6 (1.6, 4.0)	0.045
Hemoglobin (g/dL)	8.1 ± 1.7	8.0 ± 1.7	8.2 ± 1.7	8.1 ± 1.7	8.2 ± 1.8	0.145
pH	7.3 ± 0.1	7.3 ± 0.1	7.3 ± 0.1	7.3 ± 0.1	7.3 ± 0.1	< 0.001
Creatinine (mg/dL)	0.9 (0.7, 1.5)	0.8 (0.6, 1.3)	0.9 (0.6, 1.4)	0.9 (0.7, 1.4)	1.0 (0.7, 1.6)	< 0.001
White blood cell counts (×10^9/L)	16.2 (12.1, 21.7)	16.0 (11.9, 21.7)	15.2 (11.1, 20.2)	15.8 (11.8, 21.3)	16.7 (12.6, 22.1)	<0.001
Glucose (mg/dL)	133.0 (108.0, 170.0)	126.0 (103.0, 157.0)	127.0 (104.0, 160.0)	131.0 (107.0, 166.0)	141.0 (113.0, 181.0)	< 0.001
Interventions						
Mechanical ventilation use, n (%)	5,390 (92.0)	1,583 (89.6)	222 (90.6)	1,499 (91.9)	2086 (94.1)	< 0.001
Vasopressor use, n (%)	3,354 (57.2)	977 (55.3)	128 (52.2)	952 (58.3)	1,297 (58.5)	0.058
Sedative use, n (%)	422 (7.2)	118 (6.7)	18 (7.3)	115 (7)	171 (7.7)	0.646

Continuous Variables: Normally distributed variables are shown as mean (± SD), and non-normally distributed variables as median (IQR). Categorical Variables: Categorical variables are presented as counts and percentages (%). BMI, Body Mass Index; MAP, Mean Arterial Pressure; SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment; COPD, Chronic obstructive pulmonary disease; CAD, Coronary artery disease; CHF, Congestive heart failure; AFIB, Atrial fibrillation.

10.3389/fmed.2024.1462637

TABLE 3 Mortality in different BMI patients with sepsis.

Outcome	Overall	Healthy weight (18.5–24.9 kg/m²)	Underweight (<18.5 kg/m²)	Overweight (25.0–29.9 kg/m²)	Obese (≥30.0 kg/m²)	*P*-value
Male	*n* = 9,022	*n* = 2,441	*n* = 186	*n* = 3,276	*n* = 3,119	
Time in ICU (days)	3.2 (1.5,7.1)	3.3 (1.7, 7.0)	3.3 (2.0, 7.7)	3.1 (1.4, 6.5)	3.4 (1.7, 8.0)	< 0.001
28-day mortality, n (%)	1,279 (14.2)	436 (17.9)	41 (22)	413 (12.6)	389 (12.5)	< 0.001
1-year mortality, n (%)	2,403 (26.6)	838 (34.3)	99 (53.2)	770 (23.5)	696 (22.3)	< 0.001
Female	*n* = 5,861	*n* = 1767	*n* = 245	*n* = 1,632	*n* = 2,217	
Time in ICU (days)	3.7 (1.9,7.8)	3.7 (1.9, 7.8)	3.9 (1.9, 7.3)	3.6 (1.7, 7.6)	3.8 (2.0, 8.1)	0.108
28-day mortality, n (%)	1,000 (17.1)	304 (17.2)	69 (28.2)	279 (17.1)	348 (15.7)	< 0.001
1-year mortality, n (%)	1,842 (31.4)	609 (34.5)	108 (44.1)	490 (30)	635 (28.6)	< 0.001

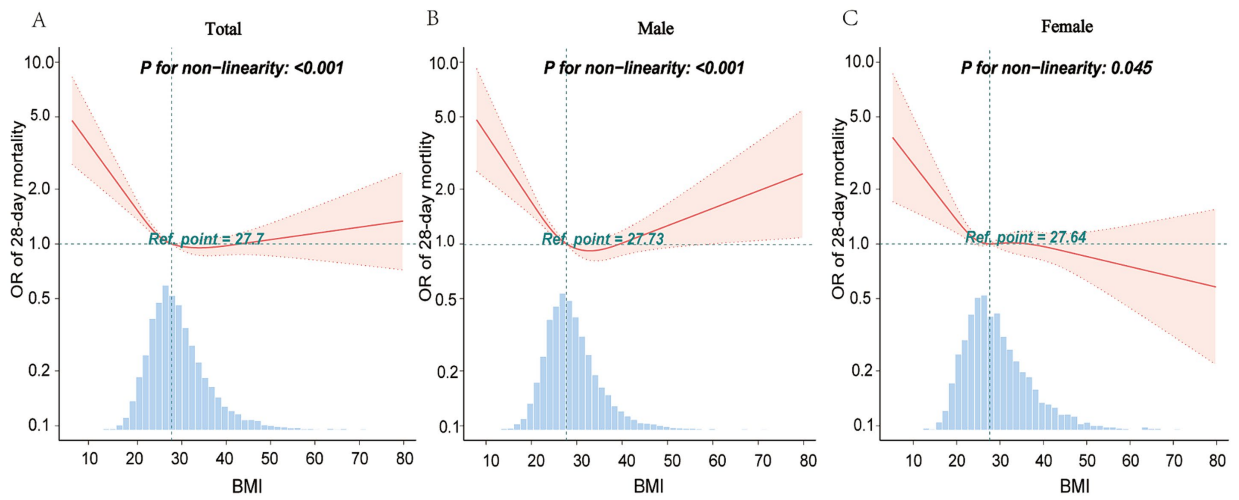

FIGURE 1
Restricted spline curves for the association between BMI and 28-day mortality. The graphs present odds ratios (ORs) for 28-day mortality, adjusting for age, gender, race, SAPS, SOFA, and the Charlson comorbidity index. It also adjusts for various comorbidities, including hypertension, stroke, congestive heart failure, renal disease, diabetes, chronic obstructive pulmonary disease, atrial fibrillation, malignancy cancer, coronary artery disease, and liver disease. Additionally, the analysis was adjusted for blood glucose levels to account for its potential impact on the outcomes. Logistic regression modeling facilitated data fitting. Solid lines on the graphs denote ORs, with shaded areas representing 95% confidence intervals (CIs). OR, odds ratio; CI, confidence interval.

interaction = 0.014). For females, being underweight was linked to 80% higher odds of 28-day mortality in comparison to having a normal weight (adjusted OR = 1.80, 95% CI = 1.28, 2.53, $p = 0.001$). No significant relationships were seen in the overweight and obese categories. In males, both overweight and obesity were linked to 33% lower odds of 28-day mortality relative to normal weight. The adjusted OR were 0.67 (95% CI = 0.57, 0.79, $p < 0.001$) for overweight and 0.67 (95% CI = 0.57, 0.80, $p < 0.001$) for obesity (Supplementary Table S6).

RCS analyses of nonlinear relationships

RCS models were developed to evaluate the link between BMI and mortality. Figure 1 depicts the dose–response curves demonstrating the correlation between BMI and 28-day all-cause mortality. The curves were obtained after performing logistic analysis and adjusting for significant covariates. The dose–response analysis demonstrated a L-shaped curve depicting the relationship between BMI and the risk of 28-day all-cause mortality (p for nonlinearity <0.001) (Figure 1A).

According to subgroup analysis, there was significant variation in the link between BMI and 28-day mortality in males versus females. RCS models were constructed for sex-stratified analysis. Figure 1B shows a U-shaped curve relationship between BMI and 28-day all-cause mortality in male patients with sepsis (p for nonlinearity <0.001). However, it reveals an L-shaped correlation between these two factors in the female patients (p for nonlinearity = 0.045) (Figure 1C). In our cohort, there were 3,418 patients with late-stage cancer. The results of a secondary analysis excluding these patients were consistent with the original findings, indicating that the inclusion of late-stage cancer patients did not significantly alter the overall results. Analyses were also conducted of the results in different age groups and Charlson comorbidity index score groups (Supplementary Figures S2, S3). This study produced curve-fitting graphs for BMI and 28-day mortality, considering various factors such as gender, age, and Charlson comorbidity index scores (Supplementary Figure S4).

Change points and associations in the BMI-mortality relationship

Table 4 presents the estimated change points associated with BMI and 28-day mortality. For the entire cohort, a BMI change point was identified at 27.89 kg/m^2. Below this change point, each 1 kg/m^2 increment in the BMI was linked with an OR of 0.94 (95% CI = 0.92, 0.96, $p < 0.001$) for mortality, indicating a protective effect. Above this BMI threshold, the OR per 1 kg/m^2 increase was neutral at 1.01 (95% CI = 1.00, 1.02, $p = 0.283$), suggesting no additional risk. Gender-specific analyses revealed a higher BMI change point for males (29.22 kg/m^2) than females (20.67 kg/m^2). The protective association below the change point was more pronounced in the males (OR = 0.93, 95% CI = 0.91, 0.95, $p < 0.001$) than in the overall cohort, with a slight increase in mortality risk above the change point (OR = 1.02, 95% CI = 1.00, 1.03, $p = 0.030$). Females exhibited a more substantial protective effect below their lower change point (OR = 0.86, 95% CI = 0.80, 0.93, $p < 0.001$), with a neutral effect above it (OR = 0.99, 95% CI = 0.98, 1.00, $p = 0.129$). Stratifying by age and Charlson comorbidity index revealed variability in change points and effect sizes but consistently showed a relation between lower BMI and higher mortality risk.

Discussion

Our study data indicate a correlation between BMI and mortality in sepsis patients. The findings suggest that low BMI may have adverse consequences, as underweight individuals exhibited higher mortality rates. Conversely, obese patients showed lower mortality rates, suggesting a potential protective effect of higher BMI. The relationship between 28-day mortality and BMI demonstrated an L-shaped curve, with significant gender-specific differences. Specifically, females exhibited an L-shaped relationship, while males exhibited a U-shaped relationship. The BMI-mortality relationship in sepsis patients was analyzed using piecewise two-line models to estimate change points and mortality associations on either side of these points. The results emphasize an intricate relationship that relies on BMI thresholds, which differ according to gender, age, and comorbidity burden, as assessed by the Charlson comorbidity index. These results emphasize the need to consider individual patient characteristics in the BMI-mortality assessment for sepsis patients. The identified BMI change points and their differential effects reinforce the concept of an "obesity paradox," suggesting a survival benefit for higher BMI up to a certain point.

The present study underscores that the correlation between BMI and 28-day mortality varies markedly between sexes—higher risk in underweight females and a protective effect in overweight and obese males. Consistent with another study, which showed that male participants with higher BMI exhibited a lower risk of mortality than female participants (12). In sepsis patients, a significant sex and BMI relationship was found in the current investigation. RCS analysis indicated a pronounced nonlinear relationship in males, characterized by a U-shaped curve. On the other hand, females exhibited an L-shaped curve, requiring a deeper understanding of the physiological mechanisms involved. The U-shaped curve in males may relate to the combined effects of visceral fat and inflammatory responses, potentially leading to increased mortality. In contrast, the L-shaped curve in females might reflect the protective role of subcutaneous fat on cardiovascular health and immunity. Hormones like estrogen and

TABLE 4 Estimated change points from piecewise two-line models in the relationship between BMI and mortality and the associations with mortality below and above the change point.

	BMI change point, kg/m^2 (95% CI)	OR per 1 kg/m^2 BMI increase below change point (95% CI)	*P*-value	OR per 1 kg/m^2 BMI increase above change point (95% CI)	*P*-value
All sepsis patients	27.89	0.94 (0.92, 0.96)	<0.001	1.01(1.00, 1.02)	0.283
Male (n = 9,022)	29.22	0.93 (0.91, 0.95)	<0.001	1.02 (1.00, 1.03)	0.030
Age					
<60 (3,207)	29.14	0.95 (0.91, 0.99)	0.014	1.02 (1.00, 1.04)	0.070
60–80 (4,442)	26.68	0.90 (0.87, 0.94)	<0.001	1.00 (0.98, 1.02)	0.936
⩾80 (1,373)	29.22	0.9 (0.88, 0.96)	<0.001	1.03 (0.96, 1.10)	0.389
Charlson comorbidity index					
<6	27.85	0.92 (0.88, 0.95)	<0.001	1.02 (1.00, 1.04)	0.063
⩾6	29.80	0.93 (0.91, 0.96)	<0.001	1.01 (0.99, 1.03)	0.317
Female (n = 5,861)	20.67	0.86 (0.80, 0.93)	<0.001	0.99 (0.98, 1.00)	0.129
Age					
<60 (1,775)	NA	1.00 (0.98, 1.02)	0.749		
60–80 (2,771)	20.76	0.85 (0.77, 0.95)	0.004	0.99 (0.97, 1.00)	0.127
⩾80 (1,315)	20.53	0.74 (0.63, 0.86)	<0.001	0.99 (0.97, 1.02)	0.696
Charlson comorbidity index					
<6	22.31	0.82 (0.76, 0.89)	<0.001	0.99 (0.97, 1.01)	0.276
⩾6	NA	0.99 (0.98, 1.01)	0.458		

OR, odds ratio; NA, not available.

testosterone, which differ between genders, could influence these patterns. Specifically, estrogen's anti-inflammatory properties might contribute to better outcomes in females (13). The present results align with growing evidence of gender-specific health responses (14, 15), highlighting the distinct impacts of different fat types on metabolic health in males and females. One study indicated that gender differences significantly impact the critical points of BMI based on body fat percentage (16). This suggests that gender differences should be considered in weight and BMI studies.

The relationship between BMI and mortality associated with sepsis in patients has been the subject of several investigations. An inverse relationship between BMI and sepsis-related mortality was shown in a meta-analysis of observational data (17), and a higher BMI has been associated with improved survival rates among older individuals with sepsis (12) but not younger individuals with sepsis (18). An analysis of a group of Japanese patients with severe sepsis revealed a higher rate of death within 28 days among individuals with lower BMI (< 18.5 kg/m^2) (19). Another meta-analysis reported decreased mortality in obese and overweight patients and increased mortality in patients who were underweight (20). Retrospective cohort research involving 55,038 adult patients diagnosed with sepsis revealed a correlation between obesity (BMI ≥ 30 kg/m^2) and survival rates in sepsis, resulting in an absolute mortality reduction (21). Mica et al. proposed that fatty tissue associated with higher BMI exerts a protective effect against inflammatory reactions like sepsis, and elevations in leptin and inflammatory biomarkers like C-reactive protein within the obese population have been considered as having a mechanistic role in the obesity paradox (22–24).

However, the inverse relationship between BMI and sepsis-related mortality has been challenged by some studies indicating the opposite. In a retrospective cohort research involving 834 individuals with sepsis admitted to the ICU, obese patients had higher mortality rates than non-obese patients (23). Impaired immune function in the obese population causes a significant increase in mortality rates (25). Population-based cohort research conducted on 0.5 million Chinese adults found that compared with a reference BMI of 22.5 to <25.0 kg/m^2, the multivariable-adjusted hazard ratios for sepsis-related mortality were 2.42 for BMI < 18.5, 1.59 for 18.5 to <20.0, 1.21 for 20.0 to <22.5, 0.97 for 25.0 to <27.5, 0.98 for 27.5 to <30.0, and 1.22 for ≥30.0 kg/m^2. The study also found increased sepsis-related mortality risk even in participants with low-and mid-normal weight (26). A two-sample Mendelian randomization study found that sepsis mortality at 28 days increased with increasing BMI; however, the effect disappeared at 90 days (27, 28). Confounders in causal inference in observational studies can lead to opposite conclusions. The correlation between BMI and mortality in sepsis patients is intricate, and the results from different research are inconclusive. Hence, the influence of BMI on sepsis-associated mortality may be contingent upon several elements and necessitates more investigation to achieve a thorough comprehension.

Although our data suggest that the overweight and obese groups had better survival chances compared to those with lower BMI, caution is warranted in interpreting these findings. Our analysis revealed that lower BMI groups had higher comorbidity scores, indicating that individuals with lower BMI may have more severe underlying health conditions, such as cachexia, which could negatively impact their prognosis. Therefore, the protective effect of a higher BMI may be partially attributable to the relatively better health status of these individuals. Although high BMI can predispose individuals to severe conditions, our findings indicate that individuals with higher BMI generally have better outcomes compared to those with severe comorbidities and lower BMI. This aligns with studies on acute respiratory distress syndrome (ARDS), where higher BMI was linked to better outcomes. Other pathophysiological mechanisms described in recent literature (29) may also explain these associations.

The study partially supports the existence of an obesity paradox in sepsis patients (30). Employing RCS, more precise ORs were derived. A lower OR was identified for BMI values of 27.7–42 kg/m^2, which correlates with an increased survival rate. Multifactorial analysis revealed a lower mortality rate in the obese population. In contrast, curve-fitting results indicated that males with higher BMI had a higher mortality rate. The lower mortality rate in the obese population may be attributed to the higher prevalence of mild obesity. However, severe obesity was linked to a higher mortality rate. The curve-fitting results suggest that a more significant proportion of people with moderate obesity was responsible for the overall decrease in the death rate.

A significant association was found between elevated BMI and decreased death rates in comparison to the healthy BMI range recommended by the WHO, and given the age of the present study population was 64.66 ± 15.55 years, this fits with previous study results (12, 18). Aging leads to a redistribution of body composition, including a decrease in lean body mass and bone density, particularly with an increase in abdominal fat mass. A study revealed that the association between BMI and mortality is influenced, to some extent, by the associations of lean body mass and fat mass with mortality (31). Body composition markers, such as waist circumference, might reveal varying impacts on specific and overall mortality causes, offering a new understanding of the negative relationship between BMI and mortality (31–33). Our dataset lacked certain reliable indicators of mortality such as lean body mass and central obesity, and future studies on mortality and sepsis should include such markers of body composition. However, analyses from a study also indicated that a higher BMI correlates with lower mortality rates in older individuals, suggesting an increased demand for nutritional reserves in older age (34). These findings underscore the consideration of age in healthy weight recommendations, emphasizing the need for further research to determine the benefits of weight gain in the elderly.

Limitations

The present study provides insights into the link between BMI and gender-specific 28-day sepsis-associated mortality in patients. However, the current research has several limitations. First, as a retrospective analysis, the study is subject to information bias, which could result in inaccuracies or incomplete data. In particular, lipid variables such as Low-Density Lipoprotein cholesterol and triglycerides, which may be strongly associated with BMI, were excluded from the primary analysis due to a high rate of missing data. The omission of these variables may limit our ability to fully adjust for metabolic factors that influence the relationship between BMI and sepsis mortality. Second, BMI was employed to measure overall obesity instead of waist circumference, which assesses central obesity. Observational studies indicate that there is a correlation between

abdominal obesity and a higher likelihood of death linked to sepsis (35). Despite using RCS to obtain more precise ORs, unmeasured confounders may still influence the BMI-mortality relationship. Moreover, this study failed to include variables such as muscle mass, fat distribution, and other aspects of body composition. These factors could impact the prognosis of sepsis patients. Other potential influencers such as lifestyle, diet, socioeconomic status, and baseline health conditions were also not examined, which could also impact the observed BMI-mortality relationship. The identification of sepsis-3 patients was primarily based on ICD-9 codes, which, although operationally convenient and readily available, may not be as precise as incorporating the SOFA score. The use of ICD-9 codes could potentially include patients with milder symptoms, which might influence the assessment of the severity of sepsis. However, to enhance the accuracy of our study's findings, our primary analysis outcomes were adjusted for the SOFA score to control for potential biases. Finally, as an observational study, causality cannot be inferred. The mechanism of the obesity paradox in sepsis is still being studied and could include inflammation (36–38), which was not controlled for in this study using inflammatory biomarkers. Despite these limitations, the study offers valuable insights into the complex link between BMI and mortality in sepsis patients. Future research should overcome these limitations with prospective designs, broader populations, and more comprehensive health metrics to further explore the role of BMI in the clinical management of sepsis.

Clinical considerations and implications

The discovery of gender-specific patterns has significant clinical implications. It underscores the importance of personalized treatment to account for gender-related physiological differences in sepsis management. Future studies should investigate the roles of inflammatory biomarkers, hormones and fat distribution in sepsis outcomes to refine gender-specific treatment approaches. The current study highlights the importance of considering gender-specific BMI and mortality relationships, reinforcing the need for personalized interventions in the management of sepsis.

Conclusion

This study uncovers the correlation between BMI and gender-specific mortality in a cohort of patients with sepsis in whom the presence of the obesity paradox was confirmed. The RCS analysis revealed a distinct L-shaped correlation between BMI and 28-day mortality. Regarding sex stratification, a U-shaped correlation was observed between BMI and 28-day mortality in male patients, whereas an L-shaped correlation was seen in females. It is necessary to conduct further studies, including many centers and large samples, in order to examine the disparities between sexes in the obesity paradox.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The collection of patient information and creation of the research resource were reviewed by the Institutional Review Board at the Beth Israel Deaconess Medical Center, who granted a waiver of informed consent and approved the data sharing initiative. Approval has been obtained from the Ethics Committee of Kunshan First People's Hospital (Ethics Number 2023–04-001-K02). All the methods and procedures carried out in this study were in accordance with relevant guidelines and regulation. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

LZ: Conceptualization, Writing – original draft, Writing – review & editing. CL: Supervision, Writing – review & editing. HH: Formal analysis, Validation, Writing – original draft, Writing – review & editing. QX: Formal analysis, Writing – original draft.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2024.1462637/full#supplementary-material

References

1. NCD Risk Factor Collaboration (NCD-RisC) Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19·2 million participants. Lancet (2016);*387*:1377–1396. doi: 10.1016/s0140-6736(16)30054-x

2. Berrington de Gonzalez A, Hartge P, Cerhan JR, Flint AJ, Hannan L, MacInnis RJ, et al. Body-mass index and mortality among 1.46 million white adults. *N Engl J Med*. (2010) 363:2211–9. doi: 10.1056/NEJMoa1000367

3. Censin JC, Peters SAE, Bovijn J, Ferreira T, Pulit SL, Mägi R, et al. Causal relationships between obesity and the leading causes of death in women and men. *PLoS Genet*. (2019) 15:e1008405. doi: 10.1371/journal.pgen.1008405

4. Fleischmann C, Scherag A, Adhikari NK, Hartog CS, Tsaganos T, Schlattmann P, et al. Assessment of global incidence and mortality of hospital-treated Sepsis. Current estimates and limitations. *Am J Respir Crit Care Med*. (2016) 193:259–72. doi: 10.1164/rccm.201504-0781OC

5. Prescott HC, Chang VW, O'Brien JM, Langa KM, Iwashyna TJ. Obesity and 1-year outcomes in older Americans with severe sepsis. *Crit Care Med*. (2014) 42:1766–74. doi: 10.1097/ccm.0000000000000336

6. Bosello O, Vanzo A. Obesity paradox and aging. *Eat Weight Disord*. (2021) 26:27–35. doi: 10.1007/s40519-019-00815-4

7. Yeo HJ, Kim TH, Jang JH, Jeon K, Oh DK, Park MH, et al. Obesity paradox and functional outcomes in Sepsis: a multicenter prospective study. *Crit Care Med*. (2023) 51:742–52. doi: 10.1097/ccm.0000000000005801

8. Li S, Hu X, Xu J, Huang F, Guo Z, Tong L, et al. Increased body mass index linked to greater short-and long-term survival in sepsis patients: a retrospective analysis of a large clinical database. *Int J Infect Dis*. (2019) 87:109–16. doi: 10.1016/j.ijid.2019.07.018

9. Gaulton TG, Marshall MacNabb C, Mikkelsen ME, Agarwal AK, Cham Sante S, Shah CV, et al. A retrospective cohort study examining the association between body mass index and mortality in severe sepsis. *Intern Emerg Med*. (2015) 10:471–9. doi: 10.1007/s11739-015-1200-1

10. Lee Y, Ahn S, Han M, Lee JA, Ahn JY, Jeong SJ, et al. The obesity paradox in younger adult patients with sepsis: analysis of the MIMIC-IV database. *Int J Obes*. (2024) 48:1223–30. doi: 10.1038/s41366-024-01523-5

11. Gu WJ, Duan XJ, Liu XZ, Cen Y, Tao LY, Lyu J, et al. Association of magnesium sulfate use with mortality in critically ill patients with sepsis: a retrospective propensity score-matched cohort study. *Br J Anaesth*. (2023) 131:861–70. doi: 10.1016/j.bja.2023.08.005

12. Li N, Tian L, Zhou Q, Miao Y, Ma H. The association between body mass index and mortality in septic older adults. *Geriatr Nurs*. (2023) 54:199–204. doi: 10.1016/j.gerinurse.2023.10.003

13. Rudnicki M, Pislaru A, Rezvan O, Rullman E, Fawzy A, Nwadozi E, et al. Transcriptomic profiling reveals sex-specific molecular signatures of adipose endothelial cells under obesogenic conditions. *iScience*. (2023) 26:105811. doi: 10.1016/j.isci.2022.105811

14. Schorr M, Dichtel LE, Gerweck AV, Valera RD, Torriani M, Miller KK, et al. Sex differences in body composition and association with cardiometabolic risk. *Biol Sex Differ*. (2018) 9:28. doi: 10.1186/s13293-018-0189-3

15. Poorthuis MHF, Sherliker P, de Borst GJ, Carter JL, Lam KBH, Jones NR, et al. Joint associations between body mass index and waist circumference with atrial fibrillation in men and women. *J Am Heart Assoc*. (2021) 10:e019025. doi: 10.1161/jaha.120.019025

16. Wollner M, Paulo Roberto BB, Alysson Roncally SC, Jurandir N, Edil LS. Accuracy of the WHO's body mass index cut-off points to measure gender-and age-specific obesity in middle-aged adults living in the city of Rio de Janeiro, Brazil. *J Public Health Res*. (2017) 6:904. doi: 10.4081/jphr.2017.904

17. Gao L, Liu JJ, Fan QC, Ling L, Ding H. Association of obesity and mortality in sepsis patients: a meta-analysis from observational evidence. *Heliyon*. (2023) 9:e19556. doi: 10.1016/j.heliyon.2023.e19556

18. Lee Y, Ahn S, Han M, Lee JA, Ahn JY, Jeong SJ, et al. Correction: the obesity paradox in younger adult patients with sepsis: analysis of the MIMIC-IV database. *Int J Obes*. (2024) 48:1353. doi: 10.1038/s41366-024-01579-3

19. Oami T, Karasawa S, Shimada T, Nakada TA, Abe T, Ogura H, et al. Association between low body mass index and increased 28-day mortality of severe sepsis in Japanese cohorts. *Sci Rep*. (2021) 11:1615. doi: 10.1038/s41598-020-80284-3

20. Bai L, Huang J, Wang D, Zhu D, Zhao Q, Li T, et al. Association of body mass index with mortality of sepsis or septic shock: an updated meta-analysis. *J Intensive Care*. (2023) 11:27. doi: 10.1186/s40560-023-00677-0

21. Pepper DJ, Demirkale CY, Sun J, Rhee C, Fram D, Eichacker P, et al. Does obesity protect against death in Sepsis? A retrospective cohort study of 55,038 adult patients. *Crit Care Med*. (2019) 47:643–50. doi: 10.1097/ccm.0000000000003692

22. Mica L, Vomela J, Keel M, Trentz O. The impact of body mass index on the development of systemic inflammatory response syndrome and sepsis in patients with polytrauma. *Injury*. (2014) 45:253–8. doi: 10.1016/j.injury.2012.11.015

23. Wang S, Liu X, Chen Q, Liu C, Huang C, Fang X. The role of increased body mass index in outcomes of sepsis: a systematic review and meta-analysis. *BMC Anesthesiol*. (2017) 17:118. doi: 10.1186/s12871-017-0405-4

24. Robinson J, Swift-Scanlan T, Salyer J, Jones T. The obesity paradox in Sepsis: a theoretical framework. *Biol Res Nurs*. (2020) 22:287–94. doi: 10.1177/1099800420905889

25. Frydrych LM, Bian G, O'Lone DE, Ward PA, Delano MJ. Obesity and type 2 diabetes mellitus drive immune dysfunction, infection development, and sepsis mortality. *J Leukoc Biol*. (2018) 104:525–34. doi: 10.1002/jlb.5vmr0118-021rr

26. Weng L, Fan J, Yu C, Guo Y, Bian Z, Wei Y, et al. Body-mass index and long-term risk of sepsis-related mortality: a population-based cohort study of 0.5 million Chinese adults. *Crit Care*. (2020) 24:534. doi: 10.1186/s13054-020-03229-2

27. Butler-Laporte G, Harroud A, Forgetta V, Richards JB. Elevated body mass index is associated with an increased risk of infectious disease admissions and mortality: a Mendelian randomization study. *Clin Microbiol Infect*. (2020) 27:710–6. doi: 10.1016/j.cmi.2020.06.014

28. Wang J, Hu Y, Zeng J, Li Q, He L, Hao W, et al. Exploring the causality between body mass index and Sepsis: a two-sample Mendelian randomization study. *Int J Public Health*. (2023) 68:1605548. doi: 10.3389/ijph.2023.1605548

29. Schetz M, de Jong A, Deane AM, Druml W, Hemelaar P, Pelosi P, et al. Obesity in the critically ill: a narrative review. *Intensive Care Med*. (2019) 45:757–69. doi: 10.1007/s00134-019-05594-1

30. Zhang L, Fang L, Lihua H, Li C. Association between obesity and 1-year mortality in septic patients: a retrospective cohort study. *BMJ Open*. (2023) 13:e066526. doi: 10.1136/bmjopen-2022-066526

31. Lee DH, Keum N, Hu FB, Orav EJ, Rimm EB, Willett WC, et al. Predicted lean body mass, fat mass, and all cause and cause specific mortality in men: prospective US cohort study. *BMJ*. (2018) 362:k2575. doi: 10.1136/bmj.k2575

32. Campbell JR, Chan ED, Falzon D, Trajman A, Keshavjee S, Leung CC, et al. Low body mass index at treatment initiation and rifampicin-resistant tuberculosis treatment outcomes: an individual participant data Meta-analysis. *Clin Infect Dis*. (2022) 75:2201–10. doi: 10.1093/cid/ciac322

33. Lv Y, Mao C, Gao X, Ji JS, Kraus VB, Yin Z, et al. The obesity paradox is mostly driven by decreased noncardiovascular disease mortality in the oldest old in China: a 20-year prospective cohort study. *Nat Aging*. (2022) 2:389–96. doi: 10.1038/s43587-022-00201-3

34. Bhaskaran K, dos-Santos-Silva I, Leon DA, Douglas IJ, Smeeth L. Association of BMI with overall and cause-specific mortality: a population-based cohort study of 3·6 million adults in the UK. *Lancet Diab Endocrinol*. (2018) 6:944–53. doi: 10.1016/s2213-8587(18)30288-2

35. Wang HE, Griffin R, Judd S, Shapiro NI, Safford MM. Obesity and risk of sepsis: a population-based cohort study. *Obesity*. (2013) 21:E762–9. doi: 10.1002/oby.20468

36. Xie H, Wei L, Zhang H, Ruan G, Liu X, Lin S, et al. Association of systemic inflammation with the obesity paradox in cancer: results from multi-cohort studies. *Inflamm Res*. (2024) 73:243–52. doi: 10.1007/s00011-023-01832-x

37. Lee JH, Hyung S, Lee J, Choi SH. Visceral adiposity and systemic inflammation in the obesity paradox in patients with unresectable or metastatic melanoma undergoing immune checkpoint inhibitor therapy: a retrospective cohort study. *J Immunother Cancer*. (2022) 10:e005226. doi: 10.1136/jitc-2022-005226

38. Drechsler C, Wanner C. The obesity paradox and the role of inflammation. *J Am Soc Nephrol*. (2016) 27:1270–2. doi: 10.1681/asn.2015101116

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Association between waist-to-hip ratio and risk of myocardial infarction: a systematic evaluation and meta-analysis

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Background: Myocardial infarction(MI) is one of the most serious health threats. Despite the increasing number of clinical methods used to predict the onset of MI, the prediction of MI is still unsatisfactory and necessitates new methods.
Objective: To systematically review observational studies from the past two decades on the association between waist-to-hip ratio (WHR) and MI risk.
Methods: Original literature on the correlation between WHR and MI was searched in PubMed, Embase, Web of Science, Cochrane Library, Science Direct, CNKI, and Wanfang up to January 31, 2024. Two researchers independently screened, extracted data, and assessed quality using the Newcastle-Ottawa Scale (NOS) and Revman5.3. Meta-analysis with Stata 16.0 calculated the combined Odd ratio (OR) for WHR and MI risk. Heterogeneity was assessed with the I^2 statistic to select the appropriate effects model. Subgroup analysis, meta-regression, sensitivity analysis, and funnel plots tested for heterogeneity and publication bias.
Results: A total of 22 observational studies were included, involving 709,093 participants. The meta-analysis showed that an elevated WHR was significantly associated with an increased risk of MI, with a pooled odds ratio (OR) of 1.98 [95% Confidence interval (CI): 1.75–2.24] and high heterogeneity ($I^2 = 91.5\%$, $P < 0.0001$). Subgroup analysis revealed a stronger association between WHR and MI in women (OR: 1.99, 95% CI: 1.43–2.77) compared to men (OR: 1.74, 95% CI: 1.36–2.22). Regional analysis indicated that the association between WHR and MI risk was highest in Asian populations (OR: 2.93 95% CI: 1.61–5.33), followed by American (OR: 1.73, 95% CI: 1.45–2.08) and European populations (OR: 2.19, 95% CI: 1.49–3.22). Sensitivity analysis demonstrated that the results remained stable after excluding one study.
Conclusion: In the general adult population, a higher WHR is a potentially significant association for MI and has predictive value for MI.

KEYWORDS

waist-to-hip ratio, myocardial infarction, central obesity, meta-analysis, incidence rate

1 Background

MI is a serious cardiovascular disease, with symptoms including severe chest pain, tightness, and difficulty breathing (1, 2). If not treated promptly, it often leads to serious complications or even death (2). Therefore, identifying valuable risk factors to help predict MI would promote healthcare. There is a large body of research indicating

that obesity-related cardiometabolic diseases are risk factors for atherosclerotic cardiovascular disease (3). Per the WHO and numerous other internationally recognized organizations like the CDC, obesity is defned by body mass index(BMI), an indirect measure of body composition. However, patients can be at an increased risk of cardiometabolic diseases if they have a normal BMI but an elevated body fat percentage (i.e., "normal weight obesity") (4). It is therefore important to consider other measures of body composition besides BMI as a measure of body fat and predict cardiometabolic risk. Dual-energy x-ray absorptiometry (DEXA) (5), bioimpedence analysis (BIA) (5), computed tomography (CT) and magnetic resonance imaging (MRI) are direct measures of body fat,while WHR, waist-to-height ratio (WHtR) and waist circumference (WC) are other indirect measures of body fat besides BMI. DEXA is a technique for measuring bone density and body fat content using the principle that different energy x-rays are absorbed to different degrees in human tissues (5). BIA is used to predict body composition based, on the electrical conductive properties of the body (5). Among these, DEXA, CT, and MRI are expensive and not readily available.BMI cannot distinguish between local and peripheral fat and does not accurately reflect the impact of WC and height (6, 7). Additionally,WC has been found in some studies to not predict the prognosis of MI well (7).

The WHR is an indicator of central obesity to predict the incidence and prognosis of cardiovascular disease. Overall, WHR as an indicator of central obesity is superior to other indicators. It not only predicts the incidence of MI but also has reference value for predicting myocardial injury before MI (8), the prognosis of MI (9, 10), and the severity of MI in patients (11, 12). The WHR is usually used as an indicator of central obesity to predict the incidence and prognosis of cardiovascular diseases. The waist circumference divided by the hip circumference defines the WHR, and the World Health Organization recommends a WHR $\geq$ 0.9 for men and $\geq$ 0.85 for women as the standard diagnostic criteria for abdominal obesity (13).

To clarify the association between WHR and MI, this paper reviews the research on the association between WHR and the risk of MI over the past two decades, summarizes the results of these studies in a meta-analysis, and aims to elucidate the relationship between WHR and MI in the general adult population. In particular, this study adds the latest data to previous studies (14, 15) and conducts a more detailed subgroup analysis, which further enriches the existing literature, especially in terms of gender, regional differences, and long-term risk assessment.

2 Materials and method

2.1 Search strategy

Computerized searches were conducted in databases such as PubMed, Embase, Web of Science, Cochrane Library, Science Direct, CNKI, and Wanfang. The English search terms included: Ratio, Waist-Hip; Ratios, Waist-Hip; Waist Hip Ratio; Waist-Hip Ratios; Waist-to-Hip Ratio; Ratio, Waist-to-Hip; Ratios, Waist-to-Hip; Waist to Hip Ratio; Waist-to-Hip Ratios; Myocardial Infarction; Cardiovascular Stroke; Cardiovascular Strokes; Stroke, Cardiovascular; Strokes, Cardiovascular; Myocardial Infarct; Myocardial Infarcts; Heart Attack; Heart Attacks. The Chinese search terms included: myocardial infarction, acute myocardial infarction, inferior wall myocardial infarction, anterior wall myocardial infarction, anteroseptal myocardial infarction, ST-segment elevation myocardial infarction, non-ST-segment elevation myocardial infarction, coronary atherosclerotic heart disease, angina, acute coronary syndrome. Two scholars from the team independently searched the above databases, with the search time up to January 31, 2024.10.21.

2.2 Inclusion and exclusion criteria for the literature

Criteria for Literature Inclusion: (1) The study subjects were the general population aged over 18 years; (2) The studies were reported in Chinese or English; (3) The studies explored the correlation between WHR and the incidence rate of MI; (4) The studies adjusted for various potential influencing factors on the association between WHR and the incidence rate of MI.

The exclusion criteria were as follows: (1) Non-clinical human trials; (2) Studies with questionable data or data that could not be extracted; (3) Literature that did not explore the WHR and the incidence rate of MI.

2.3 Literature screening

According to the specified time limit (up to January 31, 2024), two scholars independently screened the retrieved original studies. First, using Endnote to compare the titles, publication years, first authors' names, etc., to exclude duplicate literature. Then, by reading the titles and abstracts, literature unrelated to the research purpose was eliminated. Next, the remaining literature was fully searched and read, and the original studies to be finally included were confirmed according to the inclusion and exclusion criteria. In case of disagreement between the two researchers, a third researcher was involved for verification and assessment.

2.4 Data extraction

Two researchers read the papers and extracted relevant data, including the main authors' surnames, publication years, study regions, methods, sample sizes, subjects' ages, WHR, types of MI, WHR cut-off values, OR/RR/HR (95%CI), gender grouping, and adjustment factors in multivariate analysis.

2.5 Quality assessment

The final included studies covered case-control studies and cohort studies. Two methods were used for the quality

assessment of the literature: firstly, the NOS was used to assess multiple aspects of case-control studies and cohort studies, mainly including the representativeness of the studies, comparability between groups, and measurement of exposure factors, with a total score of 9 points, and studies scoring above 6 points were considered high-quality research. Subsequently, Revman5.3 software was used for assessment, focusing on random sequence generation, allocation concealment, blinding, outcome assessment blinding, completeness of outcome data, selective reporting, and other potential biases.

2.6 Data analysis

This study utilized Stata 16.0 software to perform meta-analysis and statistical analysis. The analyzed data were categorical variables, presented as OR and 95% CI to demonstrate the association between WHR and MI in the general adult population. Heterogeneity among studies was assessed using Cochrane's Q test and the I^2 statistic. A fixed-effect model was adopted if $I^2 < 50\%$; a random-effect model was used if $I^2 > 50\%$. Significant heterogeneity was considered present if the P-value of the Q test was <0.05 and $I^2 > 50\%$, in

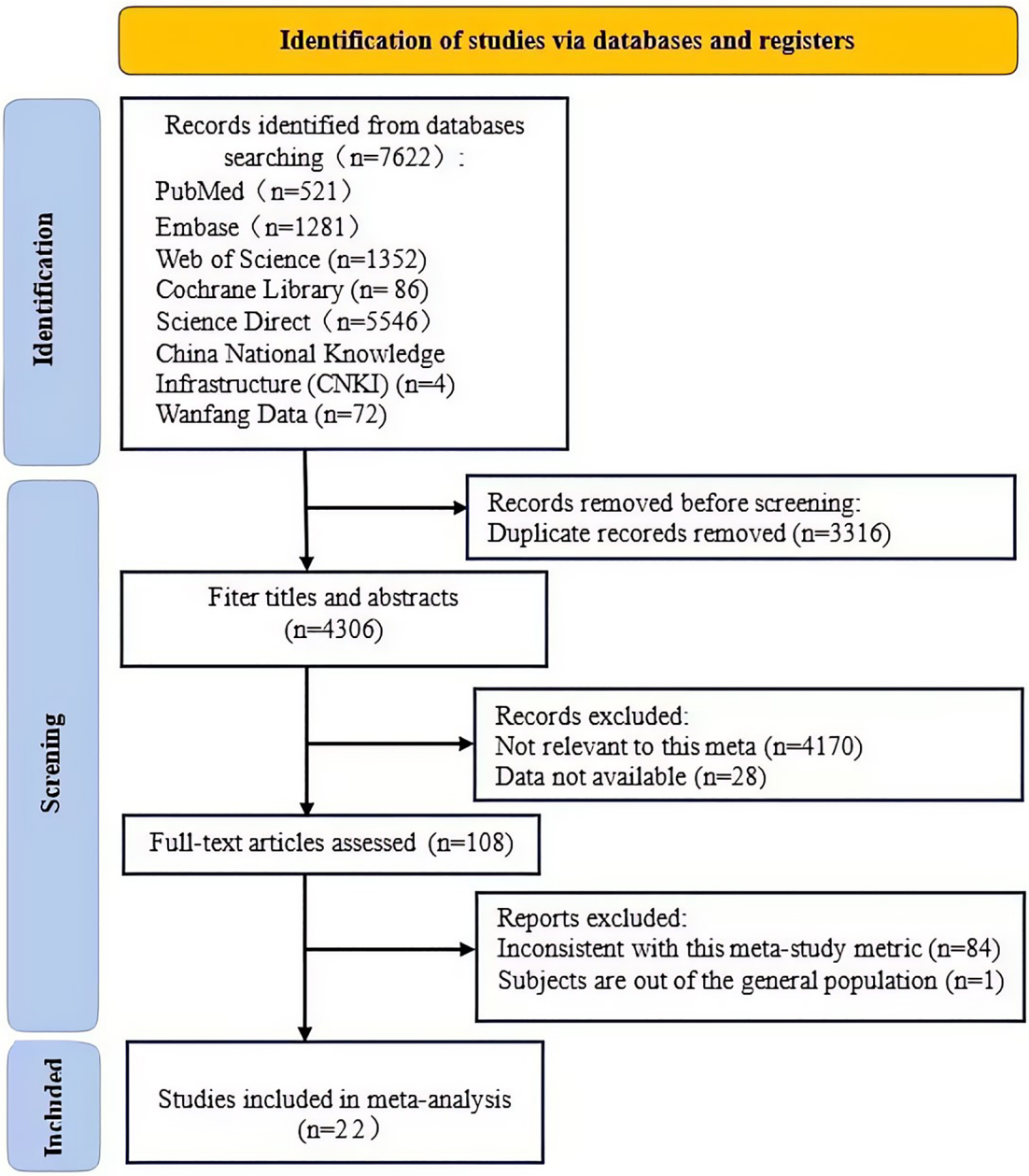

FIGURE 1
Flow diagram of search and study selection.

which case subgroup analysis and multivariate meta-regression analysis were conducted to explore the sources of heterogeneity. Subgroup analyses included gender (male, female), study region (Asia, Europe, America), type of study (case-control study, cohort study), and WHR cut-off value (<0.93, ≥0.93). The chi-square test was used to compare results within subgroups. If one subgroup had $I^2 < 50\%$ and $P > 0.05$, while another had $I^2 > 50\%$ and $P < 0.05$, it indicated that this subgroup might be the source of heterogeneity. Multivariate meta-regression analysis was also used, incorporating factors such as NOS score, average age, publication year, etc., that might affect the results into the model to investigate their potential impact on the study outcomes. If $P < 0.05$, it suggested that these factors might be sources of heterogeneity. Sensitivity analysis was conducted by excluding studies one by one to verify the stability of the results. If the OR values were stably distributed on both sides of the median line, it indicated that the results of the meta-analysis were stable. Potential publication bias was checked by visually inspecting the symmetry of the funnel plot. If the funnel plot was symmetrical, it suggested a lower risk of publication bias; if the results clustered on one side of the plot, it might indicate the presence of publication bias.

3 Results

3.1 Literature search results

We searched for English keywords in databases such as PubMed, Embase, Web of Science, Cochrane Library, Science Direct, and for Chinese keywords in CNKI and Wanfang Database, retrieving a total of 7,622 related articles. Among them, there were 521 from PubMed, 1,281 from Embase, 1,352 from Web of Science, 86 from Cochrane Library, 5,546 from Science Direct, 4 from CNKI, and 72 from Wanfang Database. After selection using Endnote and removing 3,316 duplicate articles, 4,306 remained. By reviewing titles and abstracts, and applying inclusion and exclusion criteria, 4,198 articles were screened out, including 4,170 unrelated to the study (not discussing the association between WHR and MI) and 28 unable to obtain complete data (no online access to full text, incomplete data, or obviously abnormal data). After full-text reading of the remaining 108 articles and another round of screening with inclusion and exclusion criteria, 85 articles were excluded, among which 84 had inconsistent research indicators (did not report the OR/HR/RR values of WHR and MI risk), and 1 involved a non-general population. Finally, 22 articles met the criteria (16–37). For the specific screening process, please refer to Figures 1, 2.

3.2 Literature inclusion and quality assessment

This study included 22 observational studies, comprising 7 cohort studies and 15 case-control studies, spanning from 1996 to 2023. These studies encompassed multiple countries and regions, such as Europe, Asia, and South America, with a total of 709,093 participants. The age range of the subjects was from 31.1 to 69.7 years, with WHR cut-off values ranging from 0.78 to 0.95, and the OR values indicating the association between an increase in WHR and the risk of MI ranged from 1.049 to 10.9. Among these, 8 studies also included gender subgroup analyses. When exploring the association between WHR and MI, studies typically adjusted for various factors, such as age, gender, body mass index, smoking, drinking, systolic blood pressure, total cholesterol, high-density lipoprotein, triglycerides, glycated hemoglobin, and other potential confounding factors, please refer to Table 1. The included studies encompassed seven cohort studies, which furnished data regarding the incidence of MI, methods of follow-up, and duration of follow-up. Please refer to Table 2.

To assess the quality of the literature, the NOS was used for scoring, with scores ranging from 7 to 9, indicating good overall quality of the studies. For specific assessment results, please refer

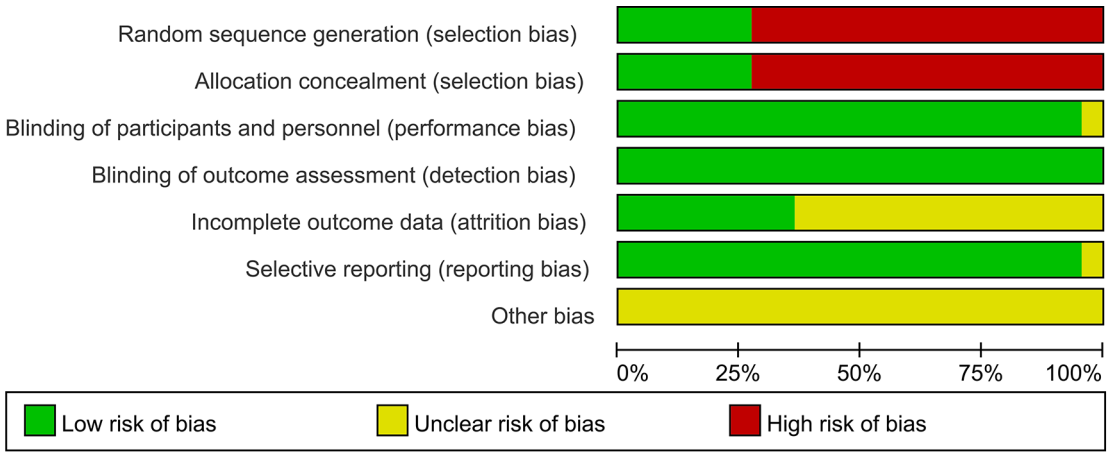

FIGURE 2
Quality assessment 1.

TABLE 1 Specific characteristics of the included studies2.

Study	Gender	WHR cutt-of value	OR or RR or HR (95%CI)	Variable adjustment	NOS
Pais P[16]	Total	0.92	3.12 (1.80–5.40)	Smoking, hypertension, income, non-vegetarianism and fasting blood sugar	7
Hertzel C[17]	Total	0.89	2.41 (1.75–3.31)	Age and gender	8
Azevedo A[18]	Male	–	2.50 (1.30–4.90)	Age, education level, family history of acute myocardial infarction and smoking	8
	Female	–	3.00 (0.60–14.60)		
Leopoldo S[19]	Total	–	1.52 (1.06–2.18)	Smoking, blood sugar, family history of coronary heart disease, low-density lipoprotein-cholesterol, hypertension, diabetes and drinking	8
Kumar P[20]	Total	–	5.20 (1.40–21.10)	History of acute myocardial infarction, smoking, BMI, hypertension, total cholesterol, serum triglyceride, LDL, HDL, blood lipid and history of apolipoprotein E4 genotyping	9
	Male	0.95			
	Female	0.80			
Yusuf S[21]	Total	–	1.77 (1.67–1.88)	Age, gender, regiom and smoking	8
	Male	0.90			
Avezum A[22]	Female	0.83			
	Total	–	3.07 (1.66–5.66)	Age and gender	7
Lanas F[23]	Total	–	2.49 (1.97–3.14)	Age, gender and smoking	7
	Male	0.90			
	Female	0.83			
Kumar A[24]	Total	0.95	3.90 (2.10–6.30)	Age, gender and hospital	8
Oliveira A[25]	Total	–		Age, educational attainment, drinking, smoking, physical activity, family history of cerebral infarction and the impact of menopause and hormone replacement therapy on women	8
	Male	0.90	10.90 (6.10–19.4)		
	Female	0.85	5.84 (3.37–10.10)		
Carević V[26]	Total	–	1.96 (1.21–3.18)	Age and gender	7
	Male	0.90			
	Female	0.83			
Kaur R[27]	Total	–	4.80 (3.20–7.30)	Confounding effects of traditional coronary risk factors	9
	Male	0.80			
	Female	0.95			
Horvei LD[28]	Male	0.95	2.50 (1.30–4.90)	Age, smoking, systolic blood pressure, total cholestrol, density lipoprotein, triglyceride, glycated hemoglobin and diabetes	8
	Female	0.85	1.09 (0.60–14.60)		
Egeland GM[29]	Male	0.91	1.22 (1.07–1.40)	Age, smoking, bmi, systolic blood pressure, diabetes and total cholesterol-hdl cholesterol ratio	9
	Male	0.91	1.09 (0.97–1.23)		
	Female	0.80	1.76 (1.37–2.25)		
	Female	0.80	1.05 (0.90–1.24)		
Rådholm K[30]	Total	–	1.08 (1.00–1.18)	Age, gender, smoking, region and randomized antihypertensive and hypoglycemic interventions	8
Peters SAE[31]	Male	–	1.36 (1.30–1.43)	Age, townshend deprivation index and smoking	9
	Female	–	1.40 (1.39–1.59)		
Hermansson J[32]	Male	1.00	1.47 (0.97–2.24)	Age and work system	7
	Female	0.88	4.17 (2.19–7.92)		
Calling S[33]	Total	0.78	1.80 (1.34–2.42)	Postmenopausal treatment,age at menopause, drinking and family history of cardiovascular disease	9
Upadhyay R[34]	Total	–	1.74 (1.02–2.94)	Age, gender and types of residential areas	8
	Male	0.95			
	Female	0.85			
Li Y[35]	Total	–	1.34 (0.46–3.85)	Gender, age, bmi, diabetes, drinking, fasting blood sugar, heart rate, hdl, hypertension, ldl, physical activity, salt consumption, systolic blood pressure and smoking	9
	Male	0.92			
	Female	0.89			
Wienbergen H[36]	–	0.87	1.57 (0.82–2.99)	Age, gender, nation, level of education, smoking, drinking, bmi, hypertension and diabetes	8
	–	0.93	6.27 (3.40–11.54)		
Zhong P[37]	Total	–	1.43 (1.15–1.78)	Age, gender, racist, income, level of education, lifestyle and history of current drug use	9
	Male	0.90			
	Female	0.85			

to Table 1. Furthermore, Revman 5.3 software was used for further quality assessment of the included studies, examining random sequence generation (selection bias), allocation concealment (selection bias), blinding among participants and personnel (performance bias), blinding in outcome assessment (detection bias), completeness of outcome data (attrition bias), selective reporting (reporting bias), and other bias factors. Given that most of the included studies were case-control studies, the quality assessment was relatively low in terms of random selection and blinding of study subjects, while other aspects

TABLE 2 Specific characteristics of the Cohort studies.

Study	Incidence of MI	Gender and year	For follow-up methods	Follow-up time(year)
Horvei LD[28]	1.13%	–	Access to medical records	15
Egeland GM[29]	2.90%	Male, year < 60	Every Norwegian resident has a unique personal identification number, which is used to identify individuals through linkage with records from the Norwegian Cause of Death Registry and the National Hospital Discharge Diagnosis Data. In clinical drug trial studies	7
	11.80%	Male, year ≥ 60		
	0.70%	Female, year < 60		
	7.40%	Female, year ≥ 60		
Rådholm K[30]	7.00%	–	Follow-up includes regular blood draws, among other procedures	9
Peters SAE[31]	1.20%		In the UK Biobank cohort study, follow-up includes regular blood draws, among other procedures.	7
Calling S33	3.10%	–	Access to medical records	17
Li Y[35]	0.46%	–	In the Kailuan prospective cohort study, questionnaires and laboratory tests are repeated every two years as part of the follow-up process.	6
Zhong P[37]	3.70%	–	In the UK Biobank cohort study, participants are followed up with regular blood draws and other procedures.	12

including performance bias, detection bias, attrition bias, reporting bias, and other biases were rated as excellent. For specific results, please see Figures 2, 3.

3.2 Publication bias

Publication Bias To assess publication bias, we conducted a funnel plot test. The funnel plot (Figure 4) shows that the studies included are relatively symmetrically distributed on the funnel plot, suggesting a lower risk of publication bias in this meta-analysis. However, caution is needed in interpretation, as the assessment of symmetry in funnel plots is somewhat subjective. For details, see Figure 4.

3.3 Data analysis results

3.3.1 Relationship between WHR and Mi

Relationship between WHR and MI The relationship between waist-hip ratio (WHR) and the risk of MI was assessed based on 22 studies of the general population. Considering the heterogeneity of the studies, a random effects model was used for analysis. Some studies were stratified by gender, age, and WHR cut-off values, with numbers 1 to 4 used to differentiate these groups within the same study. The combined results of the random effects model indicated that subjects with a higher WHR are more prone to MI compared to those with a lower WHR. The Cochrane Q test showed significant heterogeneity ($P < 0.0001$, $I^2 = 91.8\%$), and the adjusted OR was 1.98 with a 95% CI of 1.75–2.24. Detailed data can be seen in Figure 5. (Note: In the studies by Azevedo A1999, Oliveira A2010, Horvei LD2014, Peters SAE 2018, Hermansson J 2019, "1" represents the male group in the study,"2"represents the female group in the study; In the Wienbergen H 2022 study, "1"represents the group with WHR between 0.87–0.93, "2"represents the group with WHR ≥ 0.93; In Egeland GM2016, "1"represents the male group under 60 years of age,"2"represents the male group over 60 years of age, "3" represents the female group under 60 years of age, "4" represents the female group over 60 years of age.).

3.3.2 Subgroup analyses

3.3.2.1 Gender subgroup analysis

Subgroup analyses according to gender showed significant associations in both the male (OR: 1.74, 95% CI: 1.36–2.22, $P < 0.05$) and female groups (OR: 1.99, 95% CI: 1.43–2.77, $P < 0.05$), with within-group Cochrane's Q test P-values were less than 0.05 and I^2 was greater than 50%, suggesting that gender group heterogeneity did not significantly affect outcomes. The combined OR of the female group was greater than that of the male group, indicating that the association between WHR and MI was more significant in females, and thus it can be inferred that WHR is more significant in predicting MI in females. The details are shown in Figure 6. (Note: P-value <0.0001 is considered 0).

3.3.2.2 Regional subgroup analyses

According to the results of regional subgroup analysis showed that region 1 = Asia (OR: 2.93, 95% CI: 1.61–5.33, $P < 0.05$), 2 = Europe (OR: 1.73, 95% CI: 1.45–2.08, $P < 0.05$) and 3 = America (OR: 2.19, 95% CI: 1.49–3.22., $P < 0.05$), the Cochrane's Q-test P-values for within-groups were all less than 0.05, and the I^2 within-groups were all greater than 50%, suggesting that regional subgroup heterogeneity did not have a significant effect on outcomes. As shown in Figure 6. (Note: P-value <0.0001 is considered 0).

3.3.2.3 Research methods subgroup analyses

The results of the subgroup analysis according to the research methodology showed that area 1 = case-control study (OR: 2.57, 95% CI: 2.04–3.24, $P < 0.05$), 2 = cohort study (OR: 1.34, 95% CI: 1.17–1.54, $P < 0.05$), and the intragroup Cochrane's Q-test P-values were all less than 0.05 and I^2 within group was greater than 50%, indicating that heterogeneity in study method grouping did not have a significant effect on outcome. As shown in Figure 6. (Note: P-value <0.0001 is considered 0).

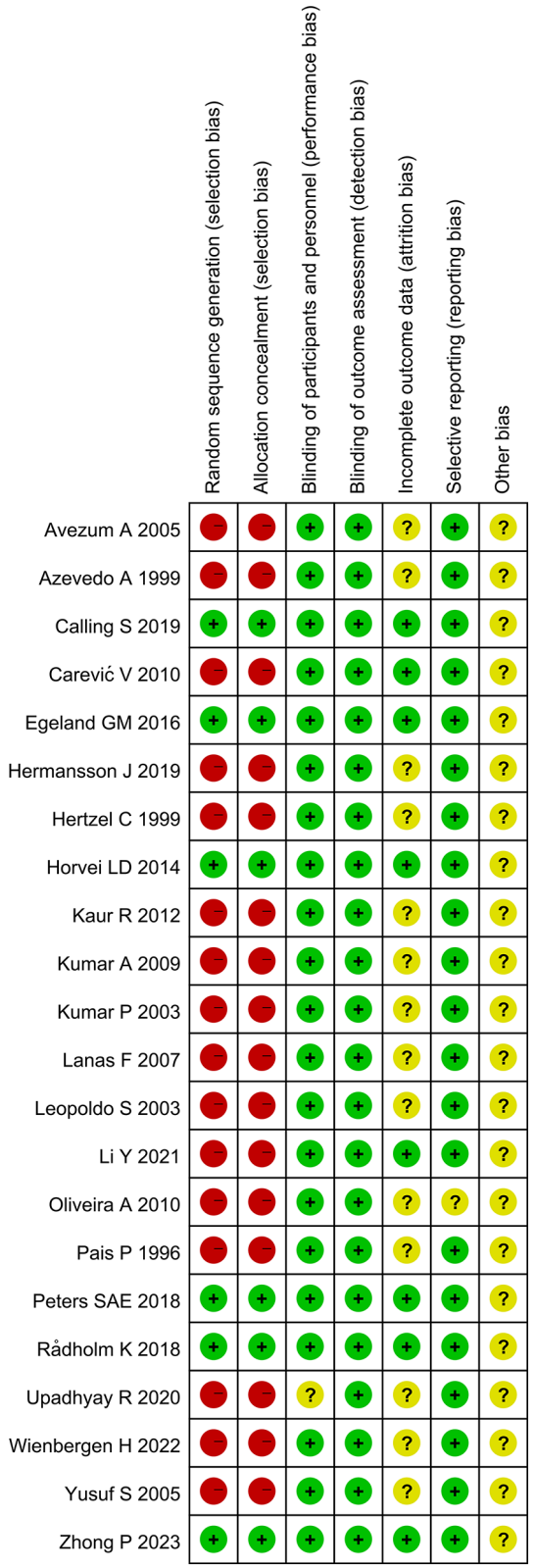

FIGURE 3
Quality assessment 2. (The green, yellow, and red colors in the fgure represent "low risk," "unclear," and "high risk," respectively.).

3.3.2.4 Subgroup analysis of WHR cut-off value

According to the results of subgroup analysis of WHR critical value showed that region 1 = WHR cut-off value <0.93 (OR: 2.05, 95% CI: 1.65–2.54, $P < 0.01$), 2 = WHR cut-off value ≥0.93 (OR: 2.69, 95% CI: 2.06–3.52, $P = 0.035$), within-group Cochrane's Q-test P-values were all less than 0.05, and within-group I^2 was greater than 50%, suggesting that heterogeneity of study WHR critical value subgroups did not have a significant effect on outcome. The combined ORs of subgroups with higher WHR critical values were greater than those of subgroups with lower WHR critical values, suggesting that higher WHRs may be more strongly associated with MI. As shown in Figure 6.

3.3.3 Multifactorial meta-regression analysis

To explore the sources of heterogeneity among studies, we further conducted a multifactorial meta-regression analysis. The results of the multifactorial meta-regression analysis showed that the P-values for all factors were above 0.05, indicating that factors such as publication year, NOS score, and age did not have a significant impact on the study results. Specific data can be referred to in Table 3. Table 3 shows that the effect size for publication year was −0.18 ($P = 0.858$), with a 95% CI ranging from −0.0551 to 0.0466, indicating that the publication year had no significant effect on the results; the effect size for the NOS score was −1.04 ($P = 0.321$), with a 95% CI ranging from −0.8493 to 0.3022, indicating that the NOS score had no significant effect on the results; the effect size for age was 0.33 ($P = 0.746$), with a 95% CI ranging from −0.0340 to 0.0461, indicating that age had no significant effect on the results. please refer to Table 3.

3.3.4 Sensitivity analysis

By sequentially excluding each study and observing the changes in the combined OR value, the results show that the combined OR values are stably distributed between 1.75 and 2.24, indicating that the meta-analysis results are relatively stable. Figure 7 shows that after the exclusion of individual studies, the CI of the combined effect size (OR) did not significantly expand or shift, suggesting that individual studies have limited impact on the overall meta-analysis results. This stability indicates that the meta-analysis results are robust and reliable. For specific results, see Figure 7.

4 Discussion

This systematic review and meta-analysis evaluated and summarized the existing evidence on the predictive value of WHR for MI over the past 20 years. We included 22 observational studies from various regions including Europe, Asia, and South America, with a total of 709,093 subjects. The quality of the studies was assessed using the NOS and Revman5.3 software, and the results indicated that the overall quality of the studies was good. The meta-analysis showed that subjects with a higher WHR had a

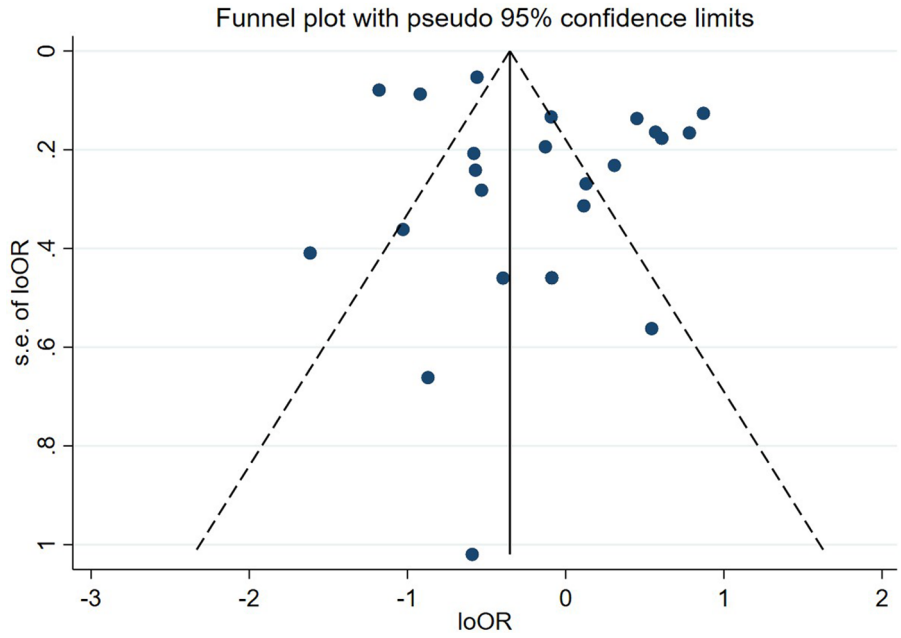

FIGURE 4
Funnel plot of publication bias among the included studies.

greater likelihood of suffering from MI compared to those with a lower WHR, with an adjusted odds ratio (OR) of 1.98, 95% CI: 1.75–2.24, $I^2 = 91.5\%$, $P < 0.0001$. This suggests that WHR is a promising factor for predicting the risk of MI and has strong predictive power. This indicates that WHR may have significant clinical relevance in identifying high-risk individuals and predicting the burden of MI in the general adult population. Furthermore, these results align with the growing literature (14, 15), supporting WHR as an important indicator in the assessment of MI risk.

In this meta-analysis, by summarizing the existing evidence on the relationship between WHR and MI over the past two decades, we found that WHR has a certain predictive role for the risk of MI. This association may be related to the following mechanisms. Firstly, central obesity refers to a relative abundance of abdominal fat compared to hip fat. A reduction in gluteal region fat is associated with a higher incidence of cardiovascular diseases (38), and abdominal fat is closely related to hypertriglyceridemia and the release of pro-inflammatory cytokines from adipose tissue, implying a higher risk of cardiovascular diseases (39, 40). Secondly, an increase in abdominal fat means an increase in visceral adipose tissue (VAT) (41), which is positively correlated with coronary atherosclerosis (42). Excessive VAT can directly or indirectly cause overactivity of the sympathetic nervous system, as well as abnormal secretion of adiponectin, leptin, and other pro-inflammatory factors, leading to dyslipidemia, a prothrombotic state, insulin resistance, and chronic inflammation, all of which are independent risk factors for cardiovascular diseases (43–47).

To explore the differences in the risk of MI associated with WHR between men and women, we conducted a subgroup analysis by gender. The results showed that an increased WHR is a stronger predictor of MI in women, although the difference is small. This result is consistent with several previous studies (14, 31, 48). In a genome-wide association study of adiposity markers by Peters SAE et al. (31), it was found that visceral fat in women had a stronger correlation with cardiac metabolic risk factors; Ramezankhani A et al. (48) found that WHR increased the risk of cardiovascular events in women more than in men; Qinqin Cao et al (14) found that the OR value of WHR for MI was higher in women in their meta-analysis. Given this result, we should pay more attention to the predictive role of WHR in women for MI, which can help medical institutions and policymakers better tailor prevention and intervention measures for different groups, such as different appropriate cut-off values for WHR in predicting MI in men and women. Researching gender differences can also promote the medical community's attention to women's cardiovascular health issues, improve the diagnosis and treatment level of women's cardiovascular diseases, and optimize the allocation of medical resources and public health policies. However, some studies have reached different conclusions (49). In the study by Hanieh Mohammadi et al. (49)], it was found that the ability of abdominal obesity to be associated with MI was lower in women than in men. Hanieh Mohammadi et al (49) believe this may be related to different fat distributions between genders. Abdominal fat is composed of VAT and subcutaneous adipose tissue (SAT), and generally, men have higher VAT than women, while women have higher SAT. Therefore, compared to women, abdominal obesity is a more direct marker of visceral fat in men, and visceral fat has a stronger correlation with cardiac metabolic risk factors. Therefore, from this mechanism, WHR should have a higher predictive value in

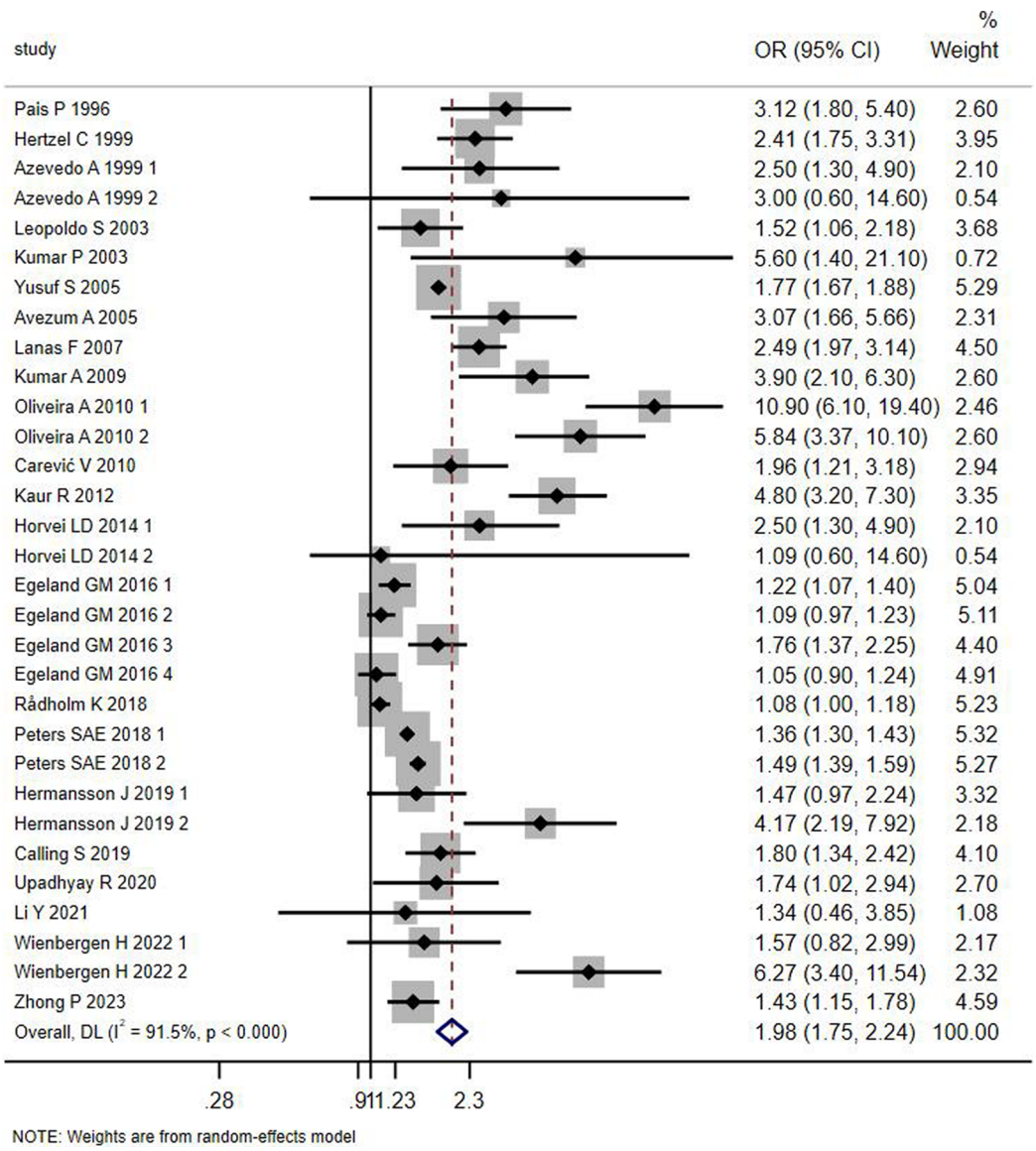

FIGURE 5
Forest plot of the meta-analysis of the association between waist-to-hip ratio and MI in the general population.

men. In summary, no studies have yet clearly explained the mechanisms related to gender differences, so conclusions related to gender need to be interpreted with caution, and further experiments need to be expanded to control more confounding factors, such as age, underlying diseases and medication, lifestyle, hormone levels, etc., to explore gender differences.

To explore whether there are regional differences in the association between WHR and the risk of MI, we conducted subgroup analyses by region. The results suggest that the association between WHR and the risk of MI may be stronger in Asian populations than in American and European populations. This could be related to a combination of factors such as racial differences, local dietary habits, socioeconomic status, medical conditions, lifestyle, and genetic factors (50–52). Particularly, the difference in body fat distribution between regions, with Asian populations tending to accumulate more visceral fat compared to Western populations (53), is closely related to the accumulation of visceral fat, WHR, and the occurrence of cardiovascular diseases. However, the study by Alenaini W et al. (54) found that the differences in visceral fat between populations across states were confounded by differences between rural and urban populations. Therefore, future large-scale prospective cohort studies could be designed to further explore the association and mechanisms between WHR and MI, controlling for confounding factors such as race, living area, body fat distribution, age, and gender.

Given these results, first, the ability of WHR to predict the risk of MI is evident, and medical professionals should consider the key role of WHR in identifying high-risk groups for MI,

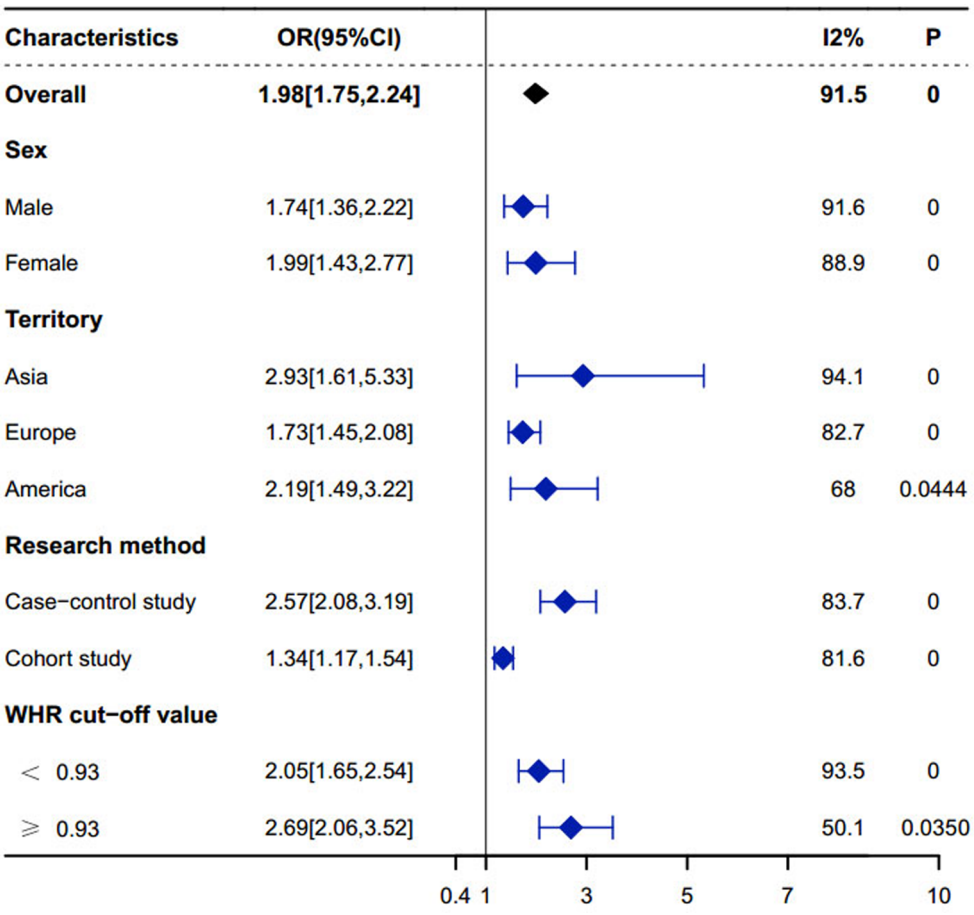

FIGURE 6
Subgroup analysis.

TABLE 3 Results of the multifactorial meta-regression analysis.

	Effect size	*p*-value	95% confidence interval	
Year of publication	−0.18	0.858	−0.0551273	0.0465668
NOS score	−1.04	0.321	−0.8493396	0.3021809
Year	0.33	0.746	−0.0339729	0.0461412

especially in women. For medical rehabilitation professionals, more attention should be paid to patients' WHR rather than just BMI. Second, in our study, the combined OR value for subgroups with higher WHR cut-off values was greater than for those with lower WHR, suggesting that a higher WHR may be more strongly associated with MI. In the future, the association between different gradients of WHR and the incidence of MI could be further explored to verify whether there is a linear correlation between WHR and the incidence of MI, and to find the WHR cut-off value with the strongest association to establish best practice guidelines. Third, the risks of a high WHR should be explained in patient health education so that patients understand that a high WHR means central obesity, which is closely related to cardiovascular diseases. Normal BMI does not mean the exclusion of the possibility of central obesity, and in daily life, attention should be paid to central obesity indicators such as WHR in addition to weight and BMI. Finally, as an indicator of central obesity, WHR has clinical significance beyond BMI and should receive more attention, especially in the prediction of MI with routine monitoring and early intervention to reduce the risk of MI. Meanwhile, effective treatment optimization needs to be combined with long-term follow-up, which can help minimize the incidence of cardiovascular events (55).

Additionally, this study also assessed the robustness of the meta-analysis results and the risk of publication bias. Sensitivity analysis results (Figure 7) show that after excluding any single study, the combined OR value remains stably distributed between 1.75 and 2.24, suggesting that individual studies have limited impact on the overall meta-analysis results. This stability indicates that the meta-analysis results are highly reliable, further supporting the research conclusion that an

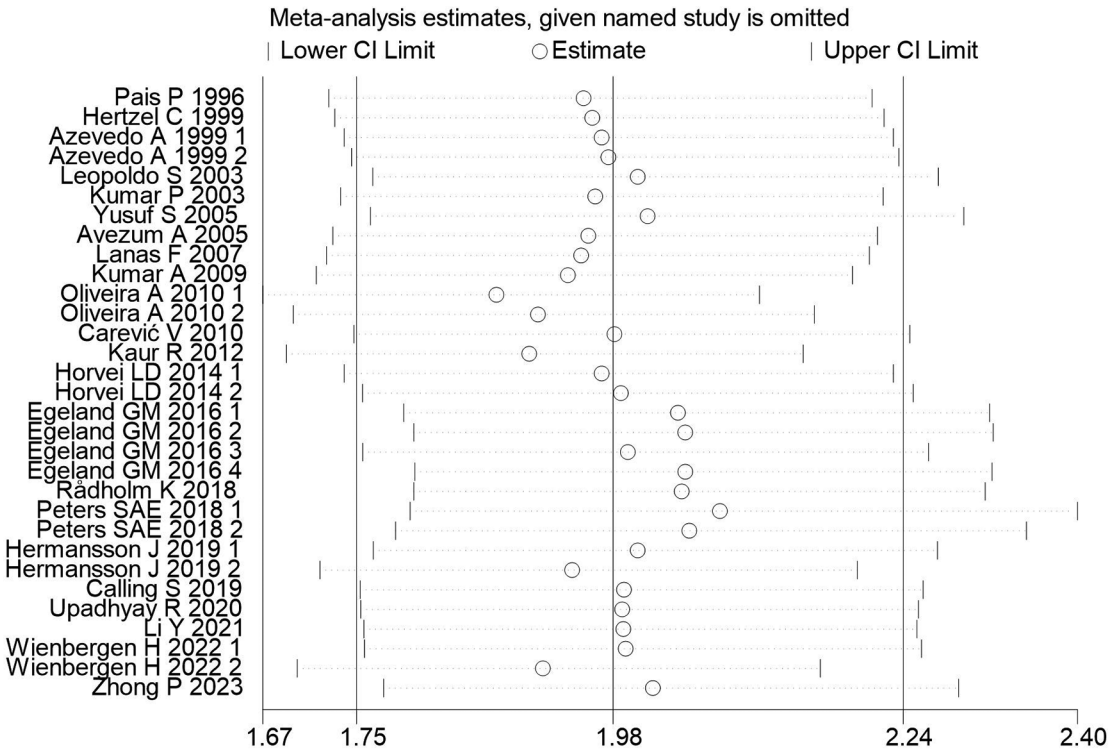

FIGURE 7
Assessment of meta-analysis stability after exclusion of individual studies. [The horizontal axis represents the exclusion of different studies, and the vertical axis represents the range of changes in the combined effect value (95% CI)].

increased WHR is significantly associated with an increased risk of MI. At the same time, funnel plot assessment (Figure 6) suggests that the included studies are relatively symmetrically distributed on the funnel plot, indicating a lower risk of publication bias. This somewhat excludes the influence of a positive result publication tendency on the meta-analysis results. However, the assessment of funnel plot symmetry still has a certain subjectivity, so the interpretation of the risk of publication bias should still be cautious.

5 Limitations

Firstly, although the combined OR values of subgroups with higher WHR critical values were found to be greater than those of subgroups with with lower WHR critical values in the subgroup analysis, suggesting that a higher WHR may be more strongly correlated with MI, this study only used categorical variable data and could not accurately explain whether there is a linear association between WHR and MI. Secondly, most of the included articles were case-control studies, and there were relatively few cohort studies with high-level evidence, so more cohort studies need to be conducted in the future to increase the credibility of the research results. Thirdly, although various sources of heterogeneity were investigated, no specific cause for heterogeneity was found. The heterogeneity of the studies reduced the reliability of this meta-analysis, and the results should be viewed with caution. Fourthly, different studies used different WHR cutoff values, and it is not possible to determine the effectiveness of a single WHR threshold for predicting MI risk. Fifthly, the sample population was limited. Most of the included studies were case-control studies often focused on a certain hospital or center, and all the studies included were published in English. Therefore, this meta-analysis does not fully represent the entire population, thus limiting the generalizability and extrapolation of the research results. Sixth, the timing of WHR data collection in case-control studies may limit the inference of causal relationships between WHR and MI. This design difference represents a limitation of the current study, potentially affecting the accuracy of event validation. Future research should prioritize prospective cohort designs to enhance the accuracy of causal inference and the assessment of the association between WHR and new incident cases of MI. Seventh, there are differences among researchers in measuring WHR, and it is recommended that future research adopt standardized techniques to objectively measure WHR.

Finally, it should be noted that there was considerable heterogeneity in this meta-analysis. Unfortunately, neither subgroup analysis nor multivariate regression analysis could find the source of heterogeneity. We believe that the reasons for this heterogeneity may include: (1) This meta-analysis combined 22

original studies, which is a large number, and there are differences in the design of each study, participant characteristics, implementation of intervention measures, and outcome measurement standards, leading to inevitable heterogeneity; (2) The heterogeneity may be related to the type of MI, differences in the standards for diagnosing MI between studies, inconsistencies in the measurement methods of WHR and covariates, and Comorbidities and and follow-up measures and different follow-up times, but since the original studies did not provide corresponding data, subgroup analysis could not be conducted; (3) Potential differences in event definitions and collection methods among different studies may lead to bias. Although heterogeneity reduces the reliability of the meta-analysis, the sensitivity analysis showed that by excluding studies one by one, regardless of which study was excluded, the combined results were stable on both sides of the median line. There was no reversal of results, and the meta-analysis therefore has stability. In summary, although there is heterogeneity in this study, it still has reference value. We should treat these results with caution, and more prospective cohort studies can be set up in the future to further verify this conclusion.

6 Conclusion

WHR is an important predictor of MI risk. Individuals with a high WHR have a signifcantly higher risk of MI than those with a low WHR, an association that is more signifcant in women.Furthermore, the higher the WHR critical value, the stronger the association with MI, suggesting apossible dose-response relationship.

Clinical medical staff should therefore pay attention to the measurement and monitoring of WHR, and use it as an important means of assessing and preventing MI risk, especially for women and individuals with a signifcantly increased WHR. Morehigh-quality prospective studies are needed to further verify thepredictive value of WHR and optimize its application in MI risk assessment.

Future research should combine WHR with other risk factors to better guide the prevention and management of MI.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

Ethics statement

This study was granted an exemption from requiring ethics approval by Jiangxi provincial People's Hospital Ethics Committee because this study was a review.

Author contributions

XZ: Data curation, Formal Analysis, Investigation, Methodology, Software, Writing – original draft, Conceptualization, Validation, Writing – review & editing. LY: Data curation, Formal Analysis, Methodology, Validation, Writing – original draft, Writing – review & editing, Investigation, Software. CX: Data curation, Formal Analysis, Investigation, Methodology, Software, Visualization, Writing – original draft, Validation, Writing – review & editing. JL: Investigation, Software, Writing – review & editing, Validation. TH: Investigation, Validation, Writing – review & editing, Resources. LL: Conceptualization, Project administration, Resources, Supervision, Visualization, Writing – review & editing, Data curation, Investigation, Validation.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Gulati R, Behfar A, Narula J, Kanwar A, Lerman A, Cooper L, et al. Acute myocardial infarction in young individuals. *Mayo Clin Proc.* (2020) 95(1):136–56. doi: 10.1016/j.mayocp.2019.05.001

2. Sagris M, Antonopoulos AS, Theofilis P, Oikonomou E, Siasos G, Tsalamandris S, et al. Risk factors profile of young and older patients with myocardial infarction. *Cardiovasc Res.* (2022) 118(10):2281–92. doi: 10.1093/cvr/cvab264

3. Hasebe T, Hasebe N. Impact of risk factors related to metabolic syndrome on acute myocardial infarction in younger patients. *Hypertension Res*. (2022) 45 (9):1447–58. doi: 10.1038/s41440-022-00951-y

4. Mohammadian Khonsari N, Khashayar P, Shahrestanaki E, Kelishadi R, Mohammadpoor Nami S, Heidari-Beni M, et al. Normal weight obesity and cardiometabolic risk factors: a systematic review and meta-analysis. *Front Endocrinol (Lausanne)*. (2022) 13:857930. doi: 10.3389/fendo.2022.857930

5. Kuriyan R. Body composition techniques. *Indian J Med Res*. (2018) 148 (5):648–58. doi: 10.4103/ijmr.IJMR_1777_18

6. Han SY, Kim NH, Kim DH, Kim YH, Park YK, Kim SM. Associations between body mass index, waist circumference, and myocardial infarction in older adults aged over 75 years: a population-based cohort study. *Medicina (Kaunas, Lithuania)*. (2022) 58:1768. doi: 10.3390/medicina58121768

7. Yoo JE, Han K, Jung JH, Hur YI, Kim YH, Kim ES, et al. Body mass index, waist circumference and cardiovascular diseases in transitional ages (40 and 66 years). *J Cachexia Sarcopenia Muscle*. (2023) 14(1):369–81. doi: 10.1002/jcsm.13138

8. Wang Z, Huang X, Li J, Liu N, Wei Q. Association between waist-hip ratio and subclinical myocardial injury in the general population: insights from the NHANES. *Front Endocrinol (Lausanne)*. (2022) 13:975327. doi: 10.3389/fendo.2022.975327

9. Zhang Y, Zhang Y, Shi Y, Dong W, Mu Y, Wang J, et al. Influence of waist-to-hip ratio on the prognosis of heart failure patients with revascularized coronary heart disease. *Front Cardiovasc Med*. (2021) 8:732200. doi: 10.3389/fcvm.2021.732200

10. Lee SH, Park JS, Kim W, Shin DG, Kim YJ, Kim DS, et al. Impact of body mass index and waist-to-hip ratio on clinical outcomes in patients with ST-segment elevation acute myocardial infarction (from the Korean acute myocardial infarction registry). *Am J Cardiol*. (2008) 102(8):957–65. doi: 10.1016/j.amjcard.2008.06.022

11. Dhar S, Das PK, Bhattacharjee B, Awal A, Ahsan SA, Shakil SS, et al. Predictive value of waist height ratio, waist hip ratio and body mass index in assessing angiographic severity of coronary artery disease in myocardial infarction patients. *Mymensingh Med J*. (2020) 29(4):906–13.

12. Jelavic MM, Babic Z, Pintaric H. The importance of two metabolic syndrome diagnostic criteria and body fat distribution in predicting clinical severity and prognosis of acute myocardial infarction. *Arch Med Sci*. (2017) 13(4):795–806. doi: 10.5114/aoms.2016.59703

13. Oumer A, Ale A, Tariku Z, Hamza A, Abera L, Seifu A. Waist-to-hip circumference and waist-to-height ratio could strongly predict glycemic control than body mass index among adult patients with diabetes in Ethiopia: ROC analysis. *PLoS One*. (2022) 17(11):e0273786. doi: 10.1371/journal.pone.0273786

14. Cao Q, Yu S, Xiong W, Li Y, Li H, Li J, et al. Waist-hip ratio as a predictor of myocardial infarction risk: a systematic review and meta-analysis. *Medicine (Baltimore)*. (2018) 97(30):e11639. doi: 10.1097/MD.0000000000011639

15. de Koning L, Merchant AT, Pogue J, Anand SS. Waist circumference and waist-to-hip ratio as predictors of cardiovascular events: meta-regression analysis of prospective studies. *Eur Heart J*. (2007) 28(7):850–6. doi: 10.1093/eurheartj/ehm026

16. Pais P, Pogue J, Gerstein H, Zachariah E, Savitha D, Jayprakash S, et al. Risk factors for acute myocardial infarction in Indians: a case-control study. *Lancet (London, England)*. (1996) 348(9024):358–63. doi: 10.1016/S0140-6736(96)02507-X

17. Gerstein HC, Pais P, Pogue J, Yusuf S. Relationship of glucose and insulin levels to the risk of myocardial infarction: a case-control study. *J Am Coll Cardiol*. (1999) 33 (3):612–9. doi: 10.1016/S0735-1097(98)00637-8

18. Azevedo A, Ramos E, von Hafe P, Barros H. Upper-body adiposity and risk of myocardial infarction. *Eur J Cardiovasc Nurs Risk*. (1999) 6(5):321–5. doi: 10.1177/204748739900600509

19. Piegas LS, Avezum A, Pereira JC, Neto JM, Hoepfner C, Farran JA, et al. Risk factors for myocardial infarction in Brazil. *Am Heart J*. (2003) 146(2):331–8. doi: 10.1016/S0002-8703(03)00181-9

20. Kumar P, Luthra K, Dwivedi M, Behl VK, Pandey RM, Misra A. Apolipoprotein E gene polymorphisms in patients with premature myocardial infarction: a case-controlled study in Asian Indians in North India. *Ann Clin Biochem*. (2003) 40(Pt 4):382–7. doi: 10.1258/000456303766477020

21. Yusuf S, Hawken S, Ounpuu S, Bautista L, Franzosi MG, Commerford P, et al. Obesity and the risk of myocardial infarction in 27,000 participants from 52 countries: a case-control study. *Lancet (London, England)*. (2005) 366(9497):1640–9. doi: 10.1016/S0140-6736(05)67663-5

22. Avezum A, Piegas LS, Pereira JC. Risk factors associated with acute myocardial infarction in the São Paulo metropolitan region: a developed region in a developing country. *Arq Bras Cardiol*. (2005) 84(3):206–13. doi: 10.1590/S0066-782X2005000300003

23. Lanas F, Avezum A, Bautista LE, Diaz R, Luna M, Islam S, et al. Risk factors for acute myocardial infarction in Latin America: the INTERHEART Latin American study. *Circulation*. (2007) 115(9):1067–74. doi: 10.1161/CIRCULATIONAHA.106.633552

24. Kumar A, Nagtilak S, Sivakanesan R, Gunasekera S. Cardiovascular risk factors in elderly normolipidemic acute myocardial infarct patients–a case controlled study from India. *Southeast Asian J Trop Med Public Health*. (2009) 40(3):581–92.

25. Oliveira A, Rodríguez-Artalejo F, Severo M, Lopes C. Indices of central and peripheral body fat: association with non-fatal acute myocardial infarction. *Int J Obes*. (2010) 34(4):733–41. doi: 10.1038/ijo.2009.281

26. Carević V, Kuzmanić M, Rumboldt M, Rumboldt Z. Predictive impact of coronary risk factors in southern Croatia: a case control study. *Coll Antropol*. (2010) 34(4):1363–8.

27. Kaur R, Das R, Ahluwalia J, Kumar RM, Talwar KK. Synergistic effect of angiotensin II type-1 receptor 1166A/C with angiotensin-converting enzyme polymorphism on risk of acute myocardial infarction in north Indians. *J Renin-Angiotensin-Aldosterone Syst*. (2012) 13(4):440–5. doi: 10.1177/1470320312438789

28. Horvei LD, Brækkan SK, Mathiesen EB, Njølstad I, Wilsgaard T, Hansen JB. Obesity measures and risk of venous thromboembolism and myocardial infarction. *Eur J Epidemiol*. (2014) 29(11):821–30. doi: 10.1007/s10654-014-9950-z

29. Egeland GM, Igland J, Vollset SE, Sulo G, Eide GE, Tell GS. High population attributable fractions of myocardial infarction associated with waist-hip ratio. *Obesity (Silver Spring, Md.)*. (2016) 24(5):1162–9. doi: 10.1002/oby.21452

30. Rådholm K, Chalmers J, Ohkuma T, Peters S, Poulter N, Hamet P, et al. Use of the waist-to-height ratio to predict cardiovascular risk in patients with diabetes: Results from the ADVANCE-ON study. *Diabetes Obes Metab*. (2018) 20 (8):1903–10. doi: 10.1111/dom.13311

31. Peters SAE, Bots SH, Woodward M. Sex differences in the association between measures of general and central adiposity and the risk of myocardial infarction: results from the UK biobank. *J Am Heart Assoc*. (2018) 7:e008507. doi: 10.1161/JAHA.117.008507

32. Hermansson J, Bøggild H, Hallqvist J, Karlsson B, Knutsson A, Nilsson T, et al. Interaction between shift work and established coronary risk factors. *Int J Occup Environ Med*. (2019) 10(2):57–65. doi: 10.15171/ijoem.2019.1466

33. Calling S, Johansson SE, Wolff M, Sundquist J, Sundquist K. The ratio of total cholesterol to high density lipoprotein cholesterol and myocardial infarction in Women's health in the Lund area (WHILA): a 17-year follow-up cohort study. *BMC Cardiovasc Disord*. (2019) 19(1):239. doi: 10.1186/s12872-019-1228-7

34. Upadhyay R, Gohel BM, Chudasama RK. Determinants of myocardial infarction in saurashtra region, gujarat: a case-control study. *Indian J Community Med*. (2020) 45 (2):154–8. doi: 10.4103/ijcmIJCM_219_19

35. Li Y, Wang C, Zhao M, Yao S, Wang M, Zhang S, et al. Effect of brachial-ankle pulse wave velocity combined with waist-to-hip ratio on cardiac and cerebrovascular events. *Am J Med Sci*. (2021) 362(2):135–42. doi: 10.1016/j.amjms.2021.02.014

36. Wienbergen H, Boakye D, Günther K, Schmucker J, Mata Marín LA, Kerniss H, et al. Lifestyle and metabolic risk factors in patients with early-onset myocardial infarction: a case-control study. *Eur J Prev Cardiol*. (2022) 29(16):2076–87. doi: 10.1093/eurjpc/zwac132

37. Zhong P, Tan S, Zhu Z, Zhu Z, Liang Y, Huang W, et al. Normal-weight central obesity and risk of cardiovascular and microvascular events in adults with prediabetes or diabetes: Chinese and British cohorts. *Diabetes Metab Res Rev*. (2023) 39(8):e3707. doi: 10.1002/dmrr.3707

38. da Silva CA, Mendes RML, de Moraes Santana N, Dos Santos NF, Pinho CPS. Dynapenic abdominal obesity in hospitalized elderly patients with acute myocardial infarction. *Exp Gerontol*. (2021) 154:111512. doi: 10.1016/j.exger.2021.111512

39. Chen GC, Arthur R, Iyengar NM, Kamensky V, Xue X, Wassertheil-Smoller S, et al. Association between regional body fat and cardiovascular disease risk among postmenopausal women with normal body mass index. *Eur Heart J*. (2019) 40 (34):2849–55. doi: 10.1093/eurheartj/ehz391

40. Matos D, Ferreira AM. The heart and the waist: relationship between abdominal fat and recurrent events after myocardial infarction. *Eur J Prev Cardiol*. (2020) 27 (18):1942–3. doi: 10.1177/2047487319900862

41. Sato R, Okada K, Akiyama E, Konishi M, Matsuzawa Y, Nakahashi H, et al. Impact of sarcopenic obesity on long-term clinical outcomes after ST-segment elevation myocardial infarction. *Atherosclerosis*. (2021) 335:135–41. doi: 10.1016/j.atherosclerosis.2021.08.038

42. Haidar A, Srikanthan P, Watson K, Allison M, Kronmal R, Horwich T. Associations between visceral fat, abdominal muscle, and coronary artery calcification: a cross-sectional analysis of the multi-ethnic study of atherosclerosis. *Am J Cardiol*. (2024) 217:77–85. doi: 10.1016/j.amjcard.2024.02.030

43. Horwich TB, Fonarow GC, Clark AL. Obesity and the obesity paradox in heart failure. *Prog Cardiovasc Dis*. (2018) 61(2):151–6. doi: 10.1016/j.pcad.2018.05.005

44. MacGregor KA, Gallagher IJ, Moran CN. Relationship between insulin sensitivity and menstrual cycle is modified by BMI, fitness, and physical activity in NHANES. *J Clin Endocrinol Metab*. (2021) 106(10):2979–90. doi: 10.1210/clinem/dgab415

45. Bermúdez V, Durán P, Rojas E, Díaz MP, Rivas J, Nava M, et al. The sick adipose tissue: new insights into defective signaling and crosstalk with the myocardium. *Front Endocrinol (Lausanne)*. (2021) 12:735070. doi: 10.3389/fendo.2021.735070

46. Wang Z, Chen J, Zhu L, Jiao S, Chen Y, Sun Y. Metabolic disorders and risk of cardiovascular diseases: a two-sample Mendelian randomization study. *BMC Cardiovasc Disord*. (2023) 23(1):529. doi: 10.1186/s12872-023-03567-3

47. Ballin M, Nordström P, Niklasson J, Nordström A. Associations of visceral adipose tissue and skeletal muscle density with incident stroke, myocardial infarction, and all-cause mortality in community-dwelling 70-year-old individuals: a

prospective cohort study. *J Am Heart Assoc*. (2021) 10:e020065. doi: 10.1161/JAHA.120.020065

48. Ramezankhani A, Azizi F, Hadaegh F. Sex differences in risk factors for coronary heart disease events: a prospective cohort study in Iran. *Sci Rep*. (2023) 13(1):22398. doi: 10.1038/s41598-023-50028-0

49. Mohammadi H, Ohm J, Discacciati A, Sundstrom J, Hambraeus K, Jernberg T, et al. Abdominal obesity and the risk of recurrent atherosclerotic cardiovascular disease after myocardial infarction. *Eur J Prev Cardiol*. (2020) 27(18):1944–52. doi: 10.1177/2047487319898019

50. Ullah M, Wahab A, Khan SU, Zaman U, Rehman Ku, Hamayun S, et al. Stent as a novel technology for coronary artery disease and their clinical manifestation. *Curr Probl Cardiol*. (2023) 48(1):101415. doi: 10.1016/j.cpcardiol.2022.101415

51. Soliman MZ, Kozman SA, Li Y, Soliman EZ, Ahmad MI. Racial differences in prevalence and impact of electrocardiographic subclinical myocardial injury risk factors. *Am J Med Sci*. (2024) 367(6):352–6. doi: 10.1016/j.amjms.2024.01.020

52. Karasik A, Lanzinger S, Chia-Hui Tan E, Yabe D, Kim DJ, Sheu WH, et al. Empagliflozin cardiovascular and renal effectiveness and safety compared to dipeptidyl peptidase-4 inhibitors across 11 countries in Europe and Asia: results from the EMPagliflozin compaRative effectIveness and SafEty (EMPRISE) study. *Diabetes Metab*. (2023) 49(2):101418. doi: 10.1016/j.diabet.2022.101418

53. Greendale GA, Han W, Finkelstein JS, Burnett-Bowie SM, Huang M, Martin D, et al. Changes in regional fat distribution and anthropometric measures across the menopause transition. *J Clin Endocrinol Metab*. (2021) 106(9):2520–34. doi: 10.1210/clinem/dgab389

54. Alenaini W, Parkinson JRC, McCarthy JP, Goldstone AP, Wilman HR, Banerjee R, et al. Ethnic differences in body fat deposition and liver fat content in two UK-based cohorts. *Obesity (Silver Spring, Md.)*. (2020) 28(11):2142–52. doi: 10.1002/oby.22948

55. Locuratolo N, Scicchitano P, Antoncecchi E, Basso P, Bonfantino VM, Brescia F, et al. Follow-up of patients after an acute coronary event: the apulia PONTE-SCA program. *G Ital Cardiol*. (2022) 23(1):63–74. doi: 10.1714/3715.37064

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Triglyceride-glucose index as a mediator of body mass index and cardiovascular disease in middle-aged and older Chinese adults: a nationally representative longitudinal cohort study

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Background: Body mass index (BMI) consistently correlates with the triglyceride-glucose (TyG) index, a marker of insulin resistance, which in turn is linked to heightened cardiovascular disease (CVD) risk. Thus, insulin resistance could potentially mediate the association between BMI and CVD risk. However, few studies have explored this mechanism in the general population.

Methods: We used data from the China Health and Retirement Longitudinal Study, which is an ongoing prospective cohort study. It initially enrolled 7233 middle-aged and older Chinese adults who were free of heart disease and stroke at baseline. The exposure variable was BMI. Incident CVD, defined as self-reported physician-diagnosed heart disease and stroke combined, served as the main outcome.

Results: Of the 7 233 participants (mean [SD] age, 58.93 [9.33] years), 3 415 (47.2%) were men. During the 7 years of follow-up, 1 411 incident CVD cases were identified. Both BMI and TyG index were associated with CVD risk (HR per 1-SD increase: BMI, 1.23; 95% CI, 1.17–1.29; TyG, 1.13; 95% CI, 1.07–1.19). The 4-way decomposition analysis show that, overweight increased CVD risk by 28% (HR [total association], 1.28; 95% CI, 1.14–1.45), with 18.1% (95% CI, 2.2%–34.0%) mediated by TyG index (HR [pure indirect association], 1.05; 95% CI, 1.02–1.09); while obesity increased CVD risk by 91% (HR [total association], 1.91; 95% CI, 1.63–2.23), with 9.5% (95% CI, 2.2%–16.7%) mediated by TyG index (HR [pure indirect association], 1.09; 95% CI, 1.03–1.15). No evidence suggested TyG index modified BMI's association with incident CVD.

Conclusions: The study revealed that the TyG index was associated to CVD risk and acted as a small partial mediator in the relationship between BMI and CVD among middle-aged and older Chinese adults. Consequently, solely addressing insulin resistance might not significantly mitigate the impact of body weight on CVD. Thus, exploring alternative pathways and potential mediators of CVD risk becomes imperative.

KEYWORDS

cardiovascular disease, triglyceride-glucose index, body mass index, mediator, 4-way decomposition approach, CHARLS

Introduction

The ongoing challenge of cardiovascular disease (CVD) persists in its impact on global health, affecting both morbidity and mortality rates, and imposing a significant burden on healthcare systems and individual well-being (1, 2). In the last thirty years, the global burden of CVD has surged, with a 92.3% increase in total prevalent cases from 271 million to 523 million and a 53.7% rise in deaths from 12.1 million to 18.6 million between 1990 and 2019 (3). This upward trend is driven by factors such as an aging population and lifestyle changes, including a higher prevalence of obesity, hypertension, and diabetes (1, 4). Although recent studies suggest a potential slowdown in the rise of overweight and obesity in high-income countries (5, 6), there is mounting evidence indicating an acceleration of this epidemic in low- and middle-income countries (7, 8). Notably, obesity globally is associated to an elevated risk of CVD across the general population (9, 10).

Although hemodynamic and metabolic factors have been suggested as factors that influence the relationship between BMI and CVD, the exact mechanisms are not yet fully understood (9, 11). Reduced insulin sensitivity constitutes a potential constituent, as evidence suggests that oxidative stress and inflammation instigated by obesity are intricately associated with the emergence of both localized and systemic insulin resistance (12). Conversely, insulin resistance is implicated in endothelial dysfunction, fostering the development of atherosclerotic plaques through alteration of gene expression patterns related to the estrogen receptor, Hence, it could potentially play a substantial role in the pathogenesis of CVD (13). It is therefore possible that insulin resistance could exert an indirect influence on CVD through BMI. TyG (triglyceride-glucose) index has been verified as a straightforward indicator of insulin resistance based on the logarithmization of glucose levels and fasting triglyceride (14). There has been evidence of a correlation between this test and the euglycemic-hyperinsulinemic clamp test, as well as a similar validity to that of the insulin resistance index calculated from the homeostatic model assessment (15). Given its accessibility and reliable performance, it is convenient for epidemiological studies to use the TyG index to measure insulin resistance as a simple proxy.

Prior studies have combined TyG index and BMI as a TyG-BMI index to examine the association with CVD and outcomes (16–19). Yet, to our knowledge, only one study has formally investigated the TyG index's role as a mediator in the connection between BMI and incident CVD within a community-based setting, with the majority of participants being coal miners (20). Limitations include population heterogeneity, absence of generalizable, or absence of interaction between BMI and TyG index.

Hence, the objective of this study was to examine whether TyG acts as a mediator or modifier in the relationship between BMI and incident CVD within the general population. Using a causal mediation approach, we disassembled the overall association of BMI with incident CVD into four components: (1) the association unaffected by mediation or interaction, (2) the association influenced solely by interaction, (3) the association driven solely by mediation, and (4) the association influenced by both mediation and interaction.

Methods

Study population

This cohort study represents a secondary analysis of the CHARLS dataset, which is an ongoing, nationally representative cohort study. Detailed information regarding the study design is available elsewhere (21, 22). In summary, the study recruited 17708 participants from June 2011 to March 2012. For the purpose of gathering information, participants underwent assessments using standardized questionnaires using a multistage stratified probability proportional-to-size sampling method. The baseline survey achieved an 80.5% response rate. Following the baseline assessment, participants underwent follow-up evaluations every 2 years.

All participants provided written informed consent to participate in the CHARLS study, which was approved by the institutional review board of Peking University. All study protocols were conducted in accordance with the principles

outlined in the Declaration of Helsinki (23), and adherence to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline was ensured for this study (24).

Assessment of exposure and mediator

The exposure variable in this study was BMI, calculated from height and weight measurements as weight in kilograms divided by height in meters squared. BMI was categorized according to the Chinese BMI classification (25) as follows: underweight (BMI <18.5 kg/m^2), normal weight (BMI 18.5–23.9 kg/m^2), overweight (BMI 24.0–27.9 kg/m^2), and obesity (BMI ≥28 kg/m^2). Trained nurses conducted the measurements of height and weight.

The mediator was TyG index, which was calculated as ln [fasting blood glucose (milligrams per deciliter) × triglycerides (milligrams per deciliter)/2) (14) and splitting into quartiles. A colorimetric enzyme assay was used at Capital Medical University's Youanmen Clinical Laboratory to determine triglycerides and fasting blood glucose levels.

Ascertainment of outcome

The primary outcome was incident CVD, the secondary outcome were incident stroke events and incident heart disease events. Consistent with prior studies (21, 26, 27), the following standardized questions were used to assess CVD events: "Have you received a diagnosis from a doctor indicating that you have experienced a heart attack, coronary heart disease, angina, congestive heart failure, or any other heart-related conditions?" or "Have you been diagnosed by a doctor with having had a stroke?" Participants who reported either a stroke or heart disease during follow-up were categorized as having experienced a CVD event. The date of CVD diagnosis was recorded between the last interview and the one in which the CVD event was reported (21, 26, 27).

Covariates

At baseline, trained interviewers used a structured questionnaire to collect information included age, sex, living residence, marital status (categorized as married or other), and educational level (grouped into no formal education, primary school, middle or high school, and college or above), self-reported smoking and drinking status (classified as never, former, or current), self-reported physician-diagnosed medical conditions (including diabetes, hypertension, dyslipidemia, and kidney disease), and the use of medications for these conditions. Metabolic factors comprised fasting plasma glucose, total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), high-sensitivity C-reactive protein (hsCRP), and serum creatinine. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration's 2009 creatinine equation (28).

Chronic kidney disease was defined as eGFR <60 mL/min/1.73 m^2 or self-reported history of chronic kidney disease. Diabetes was defined as fasting plasma glucose ≥126 mg/dL, current use of antidiabetic medication, or self-reported history of diabetes. Dyslipidemia was defined as total cholesterol ≥240 mg/dL, triglycerides ≥150 mg/dL, LDL-C ≥160 mg/dL, HDL-C <40 mg/dL, current use of lipid-lowering medication, or self-reported history of dyslipidemia. Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, current use of the antihypertensive medication, or self-reported history of hypertension.

Statistical analysis

Descriptive statistics included mean ± standard deviation (SD) and median with interquartile range (IQR). Categorical variables were depicted as n(%). Baseline characteristics were stratified by TyG index quartiles and compared using appropriate tests: χ^2 test, analysis of variance, or Kruskal-Wallis rank sum test. Missing data were imputed using the multiple imputation of chained equations method.

We first evaluated the association of BMI (both as a linear term and classification) and TyG index (both linearly and in quartiles) with CVD using Cox proportional hazard models. Additionally, we explored linear trends through entering the median value of each BMI group or TyG index quartile to test association across the various BMI groups or TyG index quartiles. We then assessed the association of BMI with mediators using linear models. All models were adjusted for age, gender, marital status, residence, education level, smoking status, and drinking status. Subsequently, we applied 4-way decomposition causal mediation techniques to estimate the controlled direct association (CDA), reference interaction (INTref), mediated interaction (INTmed), and pure indirect association (PIA) individually (29). Utilizing the framework depicted in Figure 1 (30).

To evaluate the indirect and direct association between BMI and CVD events, we utilized VanderWeele's two-stage regression method for time-to-event data (29, 31). This approach involves fitting two regression models: one for the mediator (TyG index) and another for the outcome (CVD). The outcome (CVD) was modeled using a Cox model, while the mediator (TyG index) was modeled using a linear model. We also conducted similar mediation analyses using BMI categories, treating the TyG index as a linear indicator due to its confirmed linear association with CVD risk. All models were adjusted for age, gender, marital status, residence, education level, smoking status, and drinking status. Subsequently, we used the model parameters from these models to calculated the CDA, INTref, INTmed, and PIA, estimating the proportions of the total excess association attributable to each component according to VanderWeele's derivations (29). The 95% CIs for estimates and proportion mediated were calculated by delta method (32).

We implemented several sensitivity analyses to assess the robustness. Initially, we conducted mediation analyses according to gender. Subsequently, we assessed our results using the complete dataset (6884 participants). Finally, we repeated the mediation analysis excluding participants with a BMI <18.5 kg/m^2 (6723

10.3389/fendo.2024.1431087

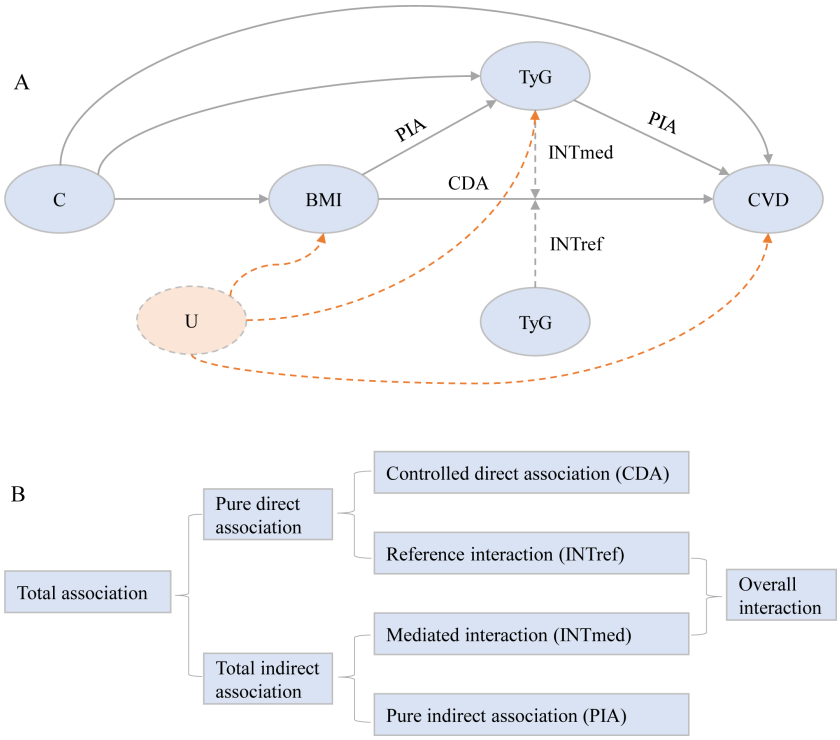

FIGURE 1
Conceptual model for the analysis of TyG index mediating the association of body mass index with incident cardiovascular disease. **(A)** The figure shows how TyG index could serve as a mediator of the association of body mass index with cardiovascular disease. The direct association between BMI and CVD is also caused by other potential mechanisms, such as hypertension, hypercholesterolemia, and/or diabetes. All statistical models were based on this structure and were adjusted for age, gender, marital status, residence, education level, smoking status, and drinking status. Following the theory of causal graphs, variables such as blood pressure (hypertension, systolic blood pressure, and diastolic blood pressure), cholesterol (total cholesterol, HDL-C, LDL-C, and dyslipidemia), renal function (kidney disease and eGFR), diabetes, glycated hemoglobin, and hsCRP represent alternative pathways that could potentially mediate aspects of the association between BMI and CVD. As such, these variables were not included as covariates in our models. C denotes the potential exposure-mediator, exposure-outcome, and mediator-outcome confounders. U denotes unmeasured confounding, which remains unavoidable in observational research settings. **(B)** Illustration of the 4-way decomposition of total association. The CDA is due to neither mediation nor interaction. The INTref is only due to interaction. The mediated INTmed is due to both mediation and interaction. PIA is only due to mediation. CDA, controlled direct association; INTref, reference interaction; INTmed, mediated interaction; PIA, pure indirect association; BMI, body mass index; CVD, cardiovascular disease; eGFR, estimated glomerular filtration ratio; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein;IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; TyG, triglyceride-glucose.

participants). We considered two-sided $P < 0.05$ as statistically significant. All analyses were carried out using R statistical software version 4.3.0 (R Foundation), and mediation analysis was performed using the CMAverse package developed by Baoyi Shi, Christine Choirat, and Linda Valeri (https://bs1125.github.io/CMAverse/index.html).

Results

Baseline characteristics

There were 17 708 participants at baseline, we excluded 777 participants below 45 years, 2 650 with baseline heart disease or stroke, 5 622 had no blood samples, 1 409 had incomplete TyG index or BMI, and 17 with extreme BMI values. Finally, 7 233 participants were included for analysis. Baseline characteristics between included and excluded participants is shown in Supplementary Table S1.

Of the 7 233 participants, the mean (SD) age at baseline was 58.93 (9.33) years; 3 415 (47.2%) were men. Participants' characteristics are presented in Table 1. At baseline, 2 088 (28.9%) participants had overweight and 755 (10.4%) had obsity, the mean (SD) TyG index was 8.65 (0.65).

Risk of CVD by TyG index or BMI

Between 2011 and 2018, 1411 participants experienced CVD events, including 1 077 heart attacks and 464 strokes, a 19.5% incidence rate. In Table 2, we show how BMI and TyG index are related to CVD events after adjusting for potential confounders (model 2), by comparing to under and normal weight, obesity was associated with a 90.0% increased risk of incident CVD (CVD: adjusted HR, 1.90; 95% CI, 1.63–2.22; stroke: adjusted HR, 2.13; 95% CI, 1.63–2.78; heart disease: adjusted HR, 1.85; 95% CI, 1.55–2.20). When modeling the TyG index as quartiles, by comparing quartile 4 with quartile 1, the adjusted HRs were 1.35 (95% CI, 1.16–

10.3389/fendo.2024.1431087

TABLE 1 Baseline characteristics participants stratified by quartiles of the TyG index.

Characteristic	Overall	TyG index [a]				P value [b]
		Quartile 1 [5.18, 8.20]	Quartile 2 (8.20, 8.57]	Quartile 3 (8.57, 9.00]	Quartile 4 (9.00, 13.00]	
No.	7233	1810	1807	1808	1808	
Age, years	58.93 ± 9.33	58.95 ± 9.66	58.86 ± 9.37	59.44 ± 9.39	58.49 ± 8.87	0.020
Gender						<0.001
Male	3415 (47.2%)	1004 (55.5%)	872 (48.3%)	770 (42.6%)	769 (42.5%)	
Female	3818 (52.8%)	806 (44.5%)	935 (51.7%)	1038 (57.4%)	1039 (57.5%)	
Marital status						0.057
Marred	6045 (83.6%)	1509 (83.4%)	1522 (84.2%)	1478 (81.7%)	1536 (85.0%)	
Other	1188 (16.4%)	301 (16.6%)	285 (15.8%)	330 (18.3%)	272 (15.0%)	
Residence						<0.001
Urban	2493 (34.5%)	514 (28.4%)	593 (32.8%)	637 (35.2%)	749 (41.4%)	
Rural	4740 (65.5%)	1296 (71.6%)	1214 (67.2%)	1171 (64.8%)	1059 (58.6%)	
Education level						0.003
No formal education	2200 (30.4%)	538 (29.7%)	534 (29.6%)	592 (32.7%)	536 (29.6%)	
Primary school	2912 (40.3%)	754 (41.7%)	751 (41.6%)	701 (38.8%)	706 (39.0%)	
Middle or high school	1915 (26.5%)	482 (26.6%)	466 (25.8%)	474 (26.2%)	493 (27.3%)	
College or above	206 (2.8%)	36 (2.0%)	56 (3.1%)	41 (2.3%)	73 (4.0%)	
Smoking status [c]						<0.001
Never	4381 (60.6%)	1001 (55.3%)	1080 (59.8%)	1131 (62.6%)	1169 (64.7%)	
Former	589 (8.1%)	151 (8.3%)	143 (7.9%)	146 (8.1%)	149 (8.2%)	
Current	2243 (31.0%)	652 (36.0%)	580 (32.1%)	523 (28.9%)	488 (27.0%)	
Drinking status [c]						<0.001
Never	4168 (57.6%)	963 (53.2%)	1022 (56.6%)	1113 (61.6%)	1070 (59.2%)	
Former	583 (8.1%)	138 (7.6%)	157 (8.7%)	155 (8.6%)	133 (7.4%)	
Current	2478 (34.3%)	709 (39.2%)	627 (34.7%)	538 (29.8%)	604 (33.4%)	
Body mass index, kg/m^2						<0.001
Under and normal (<24.0)	4390 (60.7%)	1396 (77.1%)	1212 (67.1%)	1020 (56.4%)	762 (42.1%)	
Overweight (24.0-27.9)	2088 (28.9%)	342 (18.9%)	463 (25.6%)	584 (32.3%)	699 (38.7%)	
Obesity (≥28.0)	755 (10.4%)	72 (4.0%)	132 (7.3%)	204 (11.3%)	347 (19.2%)	
History of comorbidities						
Hypertension [c]	1660 (23.0%)	281 (15.5%)	330 (18.3%)	464 (25.7%)	585 (32.4%)	<0.001
Diabetes [c]	373 (5.2%)	23 (1.3%)	49 (2.7%)	83 (4.6%)	218 (12.1%)	<0.001
Dyslipidemia [c]	557 (7.7%)	62 (3.4%)	111 (6.1%)	143 (7.9%)	241 (13.3%)	<0.001
Kidney disease [c]	362 (5.0%)	94 (5.2%)	100 (5.5%)	85 (4.7%)	83 (4.6%)	0.530
History of medication use						
Hypertension medications [c]	1198 (16.6%)	181 (10.0%)	231 (12.8%)	340 (18.8%)	446 (24.7%)	<0.001
Diabetes medications [c]	231 (3.2%)	12 (0.7%)	28 (1.5%)	46 (2.5%)	145 (8.0%)	<0.001
Dyslipidemia medications [c]	265 (3.7%)	25 (1.4%)	51 (2.8%)	67 (3.7%)	122 (6.7%)	<0.001

(Continued)

TABLE 1 Continued

Characteristic	Overall	TyG index [a]				P value [b]
		Quartile 1 [5.18, 8.20]	Quartile 2 (8.20, 8.57]	Quartile 3 (8.57, 9.00]	Quartile 4 (9.00, 13.00]	
Systole blood pressure, mmHg [c]	128.82 ± 21.02	125.04 ± 20.58	127.05 ± 20.36	130.53 ± 21.97	132.68 ± 20.31	<0.001
Diastolic blood pressure, mmHg [c]	75.02 ± 12.05	72.78 ± 11.81	74.18 ± 11.70	75.82 ± 12.41	77.31 ± 11.81	<0.001
Total cholesterol, mg/dl	194.31 ± 38.43	179.44 ± 33.30	190.32 ± 33.76	198.05 ± 36.72	209.46 ± 42.79	<0.001
HDL-C, mg/dl	51.82 ± 15.26	60.74 ± 15.17	55.22 ± 13.87	49.80 ± 13.02	41.50 ± 11.73	<0.001
LDL-C, mg/dl [c]	117.47 ± 34.60	108.88 ± 29.31	119.19 ± 30.72	124.77 ± 34.00	117.05 ± 41.28	<0.001
Glycated hemoglobin, % [c]	5.28 ± 0.81	5.08 ± 0.42	5.15 ± 0.50	5.21 ± 0.58	5.67 ± 1.28	<0.001
Median hsCRP (IQR), mg/l	1.01 (0.54, 2.14)	0.80 (0.46, 1.81)	0.89 (0.50, 1.91)	1.05 (0.59, 2.14)	1.30 (0.70, 2.59)	<0.001
eGFR, ml/min/1.73m^2 [c]	76.79 ± 43.61	75.14 ± 39.49	75.79 ± 57.26	76.42 ± 35.20	79.81 ± 38.99	0.002

Data are presented as mean ± SD or n(%), unless otherwise specified.
eGFR, estimated glomerular filtration ratio; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; TyG, triglyceride-glucose.
[a]TyG index was calculated as ln (triglycerides [milligrams per deciliter] × fasting blood glucose [milligrams per deciliter]/2).
[b]P value was based on χ^2, analysis of variance test or Kruskal-Wallis rank sum test where appropriate.
[c]Missing data: 20 for smoking status, 4 for drinking status, 32 for hypertension, 62 for diabetes, 145 for dyslipidemia, 24 for kidney disease, 33 for history of medication use for hypertension, 63 for history of medication use for diabetes, 147 for history of medication use for dyslipidemia, 70 for systole blood pressure, 71 for diastolic blood pressure, 13 for LDL-C, 61 for HbA1c, and 2 for eGFR.

TABLE 2 Risk of cardiovascular disease by TyG index or body mass index.

Outcome	No. of event/total	Model 1 [a]			Model 2 [b]		
		HR (95% CI)	P value	P for trend [c]	HR (95% CI)	P value	P for trend [c]
Cardiovascular disease							
Body mass index, kg/m^2				<0.001			<0.001
Under and normal (<24.0)	740/4390	1.00 [Reference]			1.00 [Reference]		
Overweight (24.0–27.9)	448/2088	1.30 (1.15–1.46)	<0.001		1.28 (1.14–1.44)	<0.001	
Obesity (≥28.0)	223/755	1.93 (1.66–2.25)	<0.001		1.90 (1.63–2.22)	<0.001	
Body mass index continuous [e]	1411/7233	1.23 (1.17–1.29)	<0.001		1.23 (1.17–1.29)	<0.001	
Quartiles of the TyG index [d]				<0.001			<0.001
Quartile 1 [5.18, 8.2.0]	289/1810	1.00 [Reference]			1.00 [Reference]		
Quartile 2 (8.20, 8.57]	340/1807	1.16 (0.99–1.36)	0.065		1.14 (0.98–1.34)	0.100	
Quartile 3 (8.57, 9.00]	385/1808	1.31 (1.12–1.53)	0.001		1.29 (1.10–1.50)	0.001	
Quartile 4 (9.00, 13.00]	397/1808	1.38 (1.18–1.61)	<0.001		1.35 (1.16–1.57)	<0.001	
TyG index continuous [e]	1411/7233	1.14 (1.08–1.20)	<0.001		1.13 (1.07–1.19)	<0.001	
Stroke				**<0.001**			**<0.001**
Body mass index, kg/m^2							
Under and normal (<24.0)	238/4390	1.00 [Reference]			1.00 [Reference]		
Overweight (24.0–27.9)	150/2088	1.39 (1.13–1.71)	0.002		1.42 (1.15–1.75)	0.001	
Obesity (≥28.0)	76/755	2.12 (1.63–2.76)	<0.001		2.13 (1.63–2.78)	<0.001	
Body mass index continuous [e]	464/7233	1.29 (1.19–1.40)	<0.001		1.29 (1.19–1.40)	<0.001	
Quartiles of the TyG index [d]				<0.001			<0.001

(Continued)

TABLE 2 Continued

Outcome	No. of event/total	Model 1 [a]			Model 2 [b]		
		HR (95% CI)	P value	P for trend [c]	HR (95% CI)	P value	P for trend [c]
Quartile 1 [5.18, 8.2.0]	73/1810	1.00 [Reference]			1.00 [Reference]		
Quartile 2 (8.20, 8.57]	101/1807	1.40 (1.04–1.90)	0.028		1.40 (1.03–1.89)	0.031	
Quartile 3 (8.57, 9.00]	141/1808	1.99 (1.49–2.64)	<0.001		1.96 (1.48–2.61)	<0.001	
Quartile 4 (9.00, 13.00]	149/1808	2.17 (1.64–2.88)	<0.001		2.17 (1.63–2.88)	<0.001	
TyG index continuous e	464/7233	1.31 (1.21–1.42)	<0.001		1.31 (1.21–1.42)	<0.001	
Heart disease							
Body mass index, kg/m^2				<0.001			<0.001
Under and normal (<24.0)	559/4390	1.00 [Reference]			1.00 [Reference]		
Overweight (24.0–27.9)	345/2088	1.29 (1.13–1.48)	<0.001		1.26 (1.10–1.45)	0.001	
Obesity (≥28.0)	173/755	1.90 (1.60–2.26)	<0.001		1.85 (1.55–2.20)	<0.001	
Body mass index continuous [e]	1077/7233	1.22 (1.16–1.29)	<0.001		1.21 (1.14–1.28)	<0.001	
Quartiles of the TyG index [d]				0.059			0.131
Quartile 1 [5.18, 8.2.0]	239/1810	1.00 [Reference]			1.00 [Reference]		
Quartile 2 (8.20, 8.57]	265/1807	1.08 (0.91–1.29)	0.396		1.06 (0.89–1.26)	0.525	
Quartile 3 (8.57, 9.00]	282/1808	1.13 (0.95–1.34)	0.180		1.10 (0.93–1.31)	0.266	
Quartile 4 (9.00, 13.00]	291/1808	1.18 (0.99–1.40)	0.063		1.14 (0.96–1.35)	0.143	
TyG index continuous [e]	1077/7233	1.07 (1.01–1.14)	0.016		1.06 (1.00–1.13)	0.044	

HR, hazard ratio; CI, confidence interval; TyG, triglyceride-glucose.
[a]Adjusted for age and gender.
[b]Adjusted for age, gender, marital status, residence, education level, smoking status, and drinking status.
[c]Tests for linear trend were done by modeling the median value of each group to test ordered relations across groups of body mass index or TyG index.
[d]TyG index was calculated as ln (triglycerides [milligrams per deciliter] × fasting blood glucose [milligrams per deciliter]/2).
[e]HRs given per 1-SD increase.

1.57) for incident CVD, 2.17 (95% CI, 1.63–2.88) for stroke, and 1.14 (95% CI, 0.96–1.35) for heart disease. BMI and CVD risk are linearly associated and positive (for trend, P <0.001 for CVD, stroke, and heart disease), as well as, the TyG indx (for trend, P <0.001 for CVD and stroke, P = 0.131 for heart disease).

Association of BMI and TyG index

Table 3 shows the associations of BMI with TyG index. After adjusting for potential confounders (in model 2), compared with participants with underweight and normal weight, participants with overweight and obesity had higher TyG index (overweight: adjusted β, 0.28; 95% CI, 0.25– 0.32; obesity: adjusted β, 0.47; 95% CI, 0.42–0.52).

Mediation and interaction analysis

Table 4 show the findings from 4-way decomposition model. Analysis by BMI categories yielded the adjusted HR for the total association of BMI with incident CVD was 1.28 for overweight *vs* the reference normal weight (CVD: adjusted HR, 1.28; 95% CI, 1.14–1.45;

TABLE 3 Association between body mass index and TyG index.

Body mass index, kg/m^2	No. of total	Model 1 [a]		Model 2 [b]	
		β (95% CI)	P value	β (95% CI)	P value
Under and normal (<24.0)	4390	0.00 [Reference]		0.00 [Reference]	
Overweight (24.0–27.9)	2088	0.30 (0.26–0.33)	<0.001	0.28 (0.25–0.32)	<0.001
Obesity (≥28.0)	755	0.48 (0.43–0.53)	<0.001	0.47 (0.42–0.52)	<0.001

CI, confidence interval.
[a]Adjusted for age and gender.
[b]Adjusted for age, gender, marital status, residence, education level, smoking status, and drinking status.

TABLE 4 Decomposition of the association of body mass index with incident cardiovascular disease including mediation and interaction associations by TyG index using causal mediation analysis[a].

Association component	Overweight (Ref. Under and normal weight)				Obesity (Ref. Under and normal weight)			
	HR (95% CI)	P value	Percentage of excess association (95% CI)	P value	HR (95% CI)	P value	Percentage of excess association (95% CI)	P value
Cardiovascular disease								
Total association	1.28 (1.14 to 1.45)	<0.001	100.0		1.91 (1.63 to 2.23)	<0.001	100.0	
Controlled direct association	1.28 (1.13 to 1.45)	<0.001	98.6 (27.7 to 169.6)	0.006	1.76 (1.47 to 2.10)	<0.001	83.4 (69.6 to 97.3)	<0.001
Reference interaction [b]	0.00 (-0.10 to 0.10)	0.987	0.3 (-72.2 to 72.8)	0.993	-0.00 (-0.20 to 0.19)	0.992	-0.1 (-18.3 to 18.1)	0.991
Mediated interaction [b]	-0.05 (-0.11 to 0.01)	0.129	-17.0 (-40.8 to 6.8)	0.160	0.07 (-0.10 to 0.23)	0.445	7.2 (-11.1 to 25.5)	0.440
Pure indirect association	1.05 (1.02 to 1.09)	0.004	18.1 (2.2 to 34.0)	0.025	1.09 (1.03 to 1.15)	0.004	9.5 (2.2 to 16.7)	0.011
Stroke								
Total association	1.41 (1.15 to 1.74)	0.001	100.0		2.13 (1.63 to 2.78)	<0.001	100.0	
Controlled direct association	1.35 (1.08 to 1.69)	0.008	84.0 (23.7 to 144.4)	0.006	1.72 (1.24 to 2.38)	0.001	62.3 (46.3 to 78.3)	<0.001
Reference interaction [b]	-0.02 (-0.20 to 0.17)	0.861	-4.0 (-74.9 to 67.0)	0.913	0.02 (-0.31 to 0.34)	0.907	1.7 (-22.9 to 26.4)	0.892
Mediated interaction [b]	-0.04 (-0.15 to 0.06)	0.430	-10.4 (-38.3 to 17.5)	0.465	0.19 (-0.09 to 0.47)	0.177	16.9 (-6.0 to 39.7)	0.148
Pure indirect association	1.13 (1.07 to 1.19)	<0.001	30.3 (4.1 to 56.5)	0.023	1.22 (1.11 to 1.33)	<0.001	19.1 (5.6 to 32.7)	0.006
Heart disease								
Total association	1.26 (1.10 to 1.45)	0.001	100.0		1.85 (1.55 to 2.21)	<0.001	100.0	
Controlled direct association	1.27 (1.10 to 1.47)	0.001	103.5 (10.2 to 196.8)	0.030	1.82 (1.49 to 2.23)	<0.001	96.6 (78.5 to 114.6)	<0.001
Reference interaction [a]	0.00 (-0.12 to 0.12)	0.948	1.5 (-90.7 to 93.7)	0.974	-0.00 (-0.24 to 0.24)	0.997	-0.1 (-22.4 to 22.3)	0.996
Mediated interaction [a]	-0.03 (-0.10 to 0.04)	0.428	-11.0 (-38.8 to 16.8)	0.439	0.00 (-0.20 to 0.21)	0.971	0.4 (-23.4 to 24.3)	0.971
Pure indirect association	1.02 (0.98 to 1.06)	0.440	6.0 (-9.8 to 21.7)	0.457	1.03 (0.96 to 1.10)	0.440	3.1 (-4.9 to 11.0)	0.450

HR, hazard ratio; CI, confidence interval; TyG, triglyceride-glucose.

[a]Decomposition of total associations into controlled direct association (CDA), reference interaction (INTref), mediated interaction (INTmed), and pure indirect association (PIA) was done according to the 4-way decomposition causal mediation analysis method proposed by VanderWeele. CIs were calculated according to the delta method procedure. All models were adjusted for age, gender, marital status, residence, education level, smoking status, and drinking status as depicted in the directed acyclic graph (DAG).

[b]INTref and INTmed are the estimation of additive excess relative risk due to interaction using HRs.

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stroke: adjusted HR, 1.41; 95% CI, 1.15–1.74; heart disease: adjusted HR, 1.26; 95% CI, 1.10–1.45), which increased to 1.91 for the obesity group (CVD: adjusted HR, 1.91; 95% CI, 1.63–2.23; stroke: adjusted HR, 2.13; 95% CI, 1.63–2.78; heart disease: adjusted HR, 1.85; 95% CI, 1.55–2.21). The 4 components method show that when using TyG index as a mediator, There was no evidence that BMI interacted with TyG via INTref or INTmed, and the majority of the association was direct, with the remainder being purely indirect, the proportions mediated were 18.1% for overweight (CVD: 18.1%; 95% CI, 2.2%–34.0%; stroke: 30.3%; 95% CI, 4.1%–56.5%), and 9.5% for obesity (CVD: 9.5%; 95% CI, 2.2%–16.7%; stroke: 19.1%; 95% CI, 5.6%–32.7%). Notably, for heart disease, virtually all of the association was direct, no evidence of mediation and interaction.

Subgroup and sensitivity analysis

Subgroup analysis among women (Supplementary Table S2), the proportions mediated of TyG index between BMI and CVD were increased (overweight, 37.5%; obesity, 12.3%), while the proportions mediated decreased (overweight, 6.2%; obesity, 4.6%) among men (Supplementary Table S3). Similar trends were observed in the complete data analysis (Supplementary Table S4). Moreover, the results remained consistent even after excluding participants with a BMI <18.5 kg/m^2 (Supplementary Table S5).

Discussion

In this large cohort study, we found that the TyG index independently raised the risk of CVD. Additionally, a minor portion of the BMI-CVD association was mediated by the TyG index. Epidemiological studies consistently show a positive correlation between higher BMI and subsequent CVD risk (33–37). Our study findings align with these conclusions, revealing that an increase in BMI by per 1-SD increased the risk of CVD by 23%. Moreover, stratifying participants by BMI categories revealed a 28% increased CVD risk among overweight individuals and a nearly twofold elevation (HR, 1.90) among those with obesity compared to the baseline population of normal weight. Notably, individuals classified as overweight or obese exhibit a higher propensity for developing insulin resistance, signaling early signs of disrupted glucose metabolism (38, 39). Epidemiological study have showed a direct correlation between insulin resistance and CVD, which persists independently of diabetes and is aggravated when obesity (40). Thus, BMI and CVD risk may be mediated by insulin resistance.

Our study furnishes empirical evidence substantiating the biologically conceivable conjecture that insulin resistance serves as a pivotal intermediary in the linkage between obesity and CVD. We determined that the TyG index accounted for 18.1% of the mediating proportion in cases of overweight and 9.5% in instances of general obesity. Notably, insulin resistance frequently coexists with an array of traditional risk factors including dyslipidemia, glucose dysregulation, and hypertension, all of which have been corroborated in prior research as mediators in the causal pathway between obesity and CVD (41, 42). A retrospective cohort analysis including 6 078 participants aged 60 years and older elucidated that the TyG index served as a mediator in the relationship between BMI and CVD events. Previous studies have not firmly established insulin resistance's role in BMI and CVD. However, a study involving 6078 participants aged ≥60 years showed that BMI and CVD events were the mediated by TyG index. But, the study did not furnish information regarding the proportion mediated (43). Another prospective cohort study of 94 136 participants in which most were coal miners revealed that TyG index was a mediator in the relationship between BMI and CVD events (proportion mediated: 47.81% for overweight, 37.94% for obesity) (20). Limitations include population heterogeneity, absence of generalizable, which results in a higher proportion of TyG mediation compared to our results. In contrast, our prospective analysis centered on the general population and employed a novel method to calculate the mediated proportion of TyG index. Collectively, our results, along with previous studies, suggest that controlling the TyG index may help mitigate the effects of BMI on CVD. However, this effect may not be pronounced in the Chinese general population.

The deleterious impact of BMI on CVD susceptibility is well-documented. The underlying pathophysiological mechanisms potentially involve several pathways. Adipose tissue expansion instigates heightened basal lipolysis, liberating free fatty acids (FFA), interleukins, and cytokines. These biochemical mediators contribute to cardiac dysfunction by expediting atherosclerotic progression and modulating factors implicated in inflammation, endothelial dysfunction, and coagulation abnormalities (44). Elevated FFA levels attributable to obesity precipitate insulin resistance, exacerbating impaired insulin signaling and attenuating insulin-mediated glucose uptake in skeletal muscle while augmenting hepatic glucose output (45). Moreover, a state of positive energy balance engenders adipocyte hypertrophy and ectopic fat deposition, fostering metabolic perturbations such as insulin resistance and beta-cell dysfunction (46). Additionally, the pro-inflammatory milieu associated with obesity potentiates lipolytic processes and hepatic triglyceride synthesis, exacerbating hyperlipidemia through heightened fatty acid esterification (13). Notably, insulin resistance constitutes a pivotal nexus in the interplay between obesity and CVD risk. Consequently, the TyG index emerges as a plausible intermediary linking obesity with heightened CVD susceptibility.

Our findings are notable as they stem from a comprehensive, representative cohort of the Chinese general population, with a prolonged follow-up period. This extended duration is crucial for meaningfully exploring longitudinal associations, especially those concerning obesity and CVD. Additionally, we applied a counterfactual framework to analyze mediation in an innovative way, our implementation of the 4-way decomposition approach enabled the simultaneous examination of the TyG index's role as both modifiers and mediators.

However, our study also has limitations. First, we used BMI to ascertain overweight and obesity, while widely employed and easily calculable, offers a suboptimal estimate of fat mass proportion and distribution. There was a lack of alternative metrics, such as waist circumference (47), waist-to-hip ratio (47, 48), or body fat

composition analysis (49), that could be used to quantify visceral fat more accurately. Second, the reliance on self-reporting for CVD diagnosis introduces a methodological challenge. While the CHARLS dataset lacks medical records, preventing the validation of self-reported CVD incidents, it's important to acknowledge that other large-scale studies, like the English Longitudinal Study of Ageing, have demonstrated notable agreement between self-reported CVDs and medical records (50). Third, although we cannot definitively rule out the possibility of unmeasured confounding, the observed effect sizes' magnitude makes it improbable for unmeasured confounding to entirely elucidate our observed associations. Four, the concurrent measurement of BMI and the TyG index at baseline does not guarantee temporality between exposure and mediator, introducing the potential for reverse causality. However, there exists sufficient biological rationale and explanation for BMI influencing insulin resistance (51–53). Last, due to the considerable sample size and associated costs, data on insulin resistance were not collected, preventing the use of homeostasis model assessment of insulin resistance (HOMA-IR) for reflecting insulin resistance, necessitating further investigations.

Conclusions

Our results indicate that the TyG index is valuable for identifying individuals prone to CVD development. Additionally, it acts as a minor mediator in the association between BMI and CVD within our general population cohort. Consequently, further exploration of the pathways connecting BMI to CVD is essential for comprehending disease origins and pinpointing populations that could gain the most from strategies aimed at reducing BMI.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: https://charls.pku.edu.cn/en/.

Ethics statement

The studies involving humans were approved by Ethics Review Committee of Peking University. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

Y-YG: Data curation, Formal analysis, Software, Writing – original draft. LZ: Validation, Visualization, Writing – review & editing. QL: Formal analysis, Software, Visualization, Writing – review & editing. R-RH: Project administration, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2024.1431087/full#supplementary-material

References

1. Crea F. The burden of cardiovascular risk factors: a global perspective. *Eur Heart J*. (2022) 43:2817–20. doi: 10.1093/eurheartj/ehac430

2. Collaborators GBDRF, . Global burden of 87 risk factors in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet*. (2020) 396:1223–49. doi: 10.1016/S0140-6736(20)30752-2

3. Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, et al. Global burden of cardiovascular diseases and risk factors, 1990-2019: update

from the GBD 2019 study. *J Am Coll Cardiol*. (2020) 76:2982–3021. doi: 10.1016/j.jacc.2020.11.010

4. Vaduganathan M, Mensah GA, Turco JV, Fuster V, Roth GA. The global burden of cardiovascular diseases and risk: A compass for future health. *J Am Coll Cardiol*. (2022) 80:2361–71. doi: 10.1016/j.jacc.2022.11.005

5. Chooi YC, Ding C, Magkos F. The epidemiology of obesity. *Metabolism*. (2019) 92:6–10. doi: 10.1016/j.metabol.2018.09.005

6. Collaboration NCDRF, . Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19.2 million participants. *Lancet*. (2016) 387:1377–96. doi: 10.1016/S0140-6736(16)30054-X

7. Popkin BM, Slining MM. New dynamics in global obesity facing low- and middle-income countries. *Obes Rev*. (2013) 14 Suppl 2:11–20. doi: 10.1111/obr.12102

8. Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet*. (2014) 384:766–81. doi: 10.1016/S0140-6736(14)60460-8

9. Tsao CW, Aday AW, Almarzooq ZI, Anderson CAM, Arora P, Avery CL, et al. Heart disease and stroke statistics-2023 update: A report from the american heart association. *Circulation*. (2023) 147:e93–e621. doi: 10.1161/CIR.0000000000001123

10. Force USPST, Mangione CM, Barry MJ, Nicholson WK, Cabana M, Coker TR, et al. Behavioral counseling interventions to promote a healthy diet and physical activity for cardiovascular disease prevention in adults without cardiovascular disease risk factors: US preventive services task force recommendation statement. *JAMA*. (2022) 328:367–74. doi: 10.1001/jama.2022.10951

11. Makarem N, German CA, Zhang Z, Diaz KM, Palta P, Duncan DT, et al. Rest-activity rhythms are associated with prevalent cardiovascular disease, hypertension, obesity, and central adiposity in a nationally representative sample of US adults. *J Am Heart Assoc*. (2024) 13:e032073. doi: 10.1161/JAHA.122.032073

12. Steppan CM, Bailey ST, Bhat S, Brown EJ, Banerjee RR, Wright CM, et al. The hormone resistin links obesity to diabetes. *Nature*. (2001) 409:307–12. doi: 10.1038/35053000

13. Ormazabal V, Nair S, Elfeky O, Aguayo C, Salomon C, Zuniga FA. Association between insulin resistance and the development of cardiovascular disease. *Cardiovasc Diabetol*. (2018) 17:122. doi: 10.1186/s12933-018-0762-4

14. Simental-Mendia LE, Rodriguez-Moran M, Guerrero-Romero F. The product of fasting glucose and triglycerides as surrogate for identifying insulin resistance in apparently healthy subjects. *Metab Syndr Relat Disord*. (2008) 6:299–304. doi: 10.1089/met.2008.0034

15. Guerrero-Romero F, Simental-Mendia LE, Gonzalez-Ortiz M, Martinez-Abundis E, Ramos-Zavala MG, Hernandez-Gonzalez SO, et al. The product of triglycerides and glucose, a simple measure of insulin sensitivity. Comparison with the euglycemic-hyperinsulinemic clamp. *J Clin Endocrinol Metab*. (2010) 95:3347–51. doi: 10.1210/jc.2010-0288

16. Dang K, Wang X, Hu J, Zhang Y, Cheng L, Qi X, et al. The association between triglyceride-glucose index and its combination with obesity indicators and cardiovascular disease: NHANES 2003-2018. *Cardiovasc Diabetol*. (2024) 23:8. doi: 10.1186/s12933-023-02115-9

17. Yang X, Li K, Wen J, Yang C, Li Y, Xu G, et al. Association of the triglyceride glucose-body mass index with the extent of coronary artery disease in patients with acute coronary syndromes. *Cardiovasc Diabetol*. (2024) 23:24. doi: 10.1186/s12933-024-02124-2

18. Li F, Wang Y, Shi B, Sun S, Wang S, Pang S, et al. Association between the cumulative average triglyceride glucose-body mass index and cardiovascular disease incidence among the middle-aged and older population: a prospective nationwide cohort study in China. *Cardiovasc Diabetol*. (2024) 23:16. doi: 10.1186/s12933-023-02114-w

19. Huo RR, Zhai L, Liao Q, You XM. Changes in the triglyceride glucose-body mass index estimate the risk of stroke in middle-aged and older Chinese adults: a nationwide prospective cohort study. *Cardiovasc Diabetol*. (2023) 22:254. doi: 10.1186/s12933-023-01983-5

20. Tian X, Chen S, Wang P, Xu Q, Zhang Y, Luo Y, et al. Insulin resistance mediates obesity-related risk of cardiovascular disease: a prospective cohort study. *Cardiovasc Diabetol*. (2022) 21:289. doi: 10.1186/s12933-022-01729-9

21. Zhao Y, Hu Y, Smith JP, Strauss J, Yang G. Cohort profile: the China health and retirement longitudinal study (CHARLS). *Int J Epidemiol*. (2014) 43:61–8. doi: 10.1093/ije/dys203

22. Gu D, Dupre ME. *Encyclopedia of gerontology and population aging*. Cham, Switzerland: Springer (2021).

23. World Medical A. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*. (2013) 310:2191–4. doi: 10.1001/jama.2013.281053

24. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *BMJ*. (2007) 335:806–8. doi: 10.1136/bmj.39335.541782.AD

25. Pan XF, Wang L, Pan A. Epidemiology and determinants of obesity in China. *Lancet Diabetes Endocrinol*. (2021) 9:373–92. doi: 10.1016/S2213-8587(21)00045-0

26. Gao K, Cao LF, Ma WZ, Gao YJ, Luo MS, Zhu J, et al. Association between sarcopenia and cardiovascular disease among middle-aged and older adults: Findings from the China health and retirement longitudinal study. *EClinicalMedicine*. (2022) 44:101264. doi: 10.1016/j.eclinm.2021.101264

27. Li H, Zheng D, Li Z, Wu Z, Feng W, Cao X, et al. Association of depressive symptoms with incident cardiovascular diseases in middle-aged and older chinese adults. *JAMA Netw Open*. (2019) 2:e1916591. doi: 10.1001/jamanetworkopen.2019.16591

28. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. (2009) 150:604–12. doi: 10.7326/0003-4819-150-9-200905050-00006

29. VanderWeele TJ. A unification of mediation and interaction: a 4-way decomposition. *Epidemiology*. (2014) 25:749–61. doi: 10.1097/EDE.0000000000000121

30. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. *Epidemiology*. (1999) 10:37–48.

31. VanderWeele TJ. Causal mediation analysis with survival data. *Epidemiology*. (2011) 22:582–5. doi: 10.1097/EDE.0b013e31821db37e

32. Valeri L, Vanderweele TJ. Mediation analysis allowing for exposure-mediator interactions and causal interpretation: theoretical assumptions and implementation with SAS and SPSS macros. *Psychol Methods*. (2013) 18:137–50. doi: 10.1037/a0031034

33. Almuwaqqat Z, Hui Q, Liu C, Zhou JJ, Voight BF, Ho YL, et al. Long-term body mass index variability and adverse cardiovascular outcomes. *JAMA Netw Open*. (2024) 7:e243062. doi: 10.1001/jamanetworkopen.2024.3062

34. Powell-Wiley TM, Poirier P, Burke LE, Despres JP, Gordon-Larsen P, Lavie CJ, et al. Obesity and cardiovascular disease: A scientific statement from the american heart association. *Circulation*. (2021) 143:e984–e1010. doi: 10.1161/CIR.0000000000000973

35. Collaborators GBDO, Afshin A, Forouzanfar MH, Reitsma MB, Sur P, Estep K, et al. Health effects of overweight and obesity in 195 countries over 25 years. *N Engl J Med*. (2017) 377:13–27. doi: 10.1056/NEJMoa1614362

36. Kong KA, Park J, Hong SH, Hong YS, Sung YA, Lee H. Associations between body mass index and mortality or cardiovascular events in a general Korean population. *PloS One*. (2017) 12:e0185024. doi: 10.1371/journal.pone.0185024

37. Nordestgaard BG, Palmer TM, Benn M, Zacho J, Tybjaerg-Hansen A, Davey Smith G, et al. The effect of elevated body mass index on ischemic heart disease risk: causal estimates from a Mendelian randomisation approach. *PloS Med*. (2012) 9:e1001212. doi: 10.1371/journal.pmed.1001212

38. Liao C, Gao W, Cao W, Lv J, Yu C, Wang S, et al. Associations of metabolic/obesity phenotypes with insulin resistance and C-reactive protein: results from the CNTR study. *Diabetes Metab Syndr Obes*. (2021) 14:1141–51. doi: 10.2147/DMSO.S298499

39. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. *Diabetes*. (1988) 37:1595–607. doi: 10.2337/diab.37.12.1595

40. Zhao Q, Zhang TY, Cheng YJ, Ma Y, Xu YK, Yang JQ, et al. Impacts of triglyceride-glucose index on prognosis of patients with type 2 diabetes mellitus and non-ST-segment elevation acute coronary syndrome: results from an observational cohort study in China. *Cardiovasc Diabetol*. (2020) 19:108. doi: 10.1186/s12933-020-01086-5

41. Bakhtiyari M, Schmidt N, Hadaegh F, Khalili D, Mansournia N, Asgari S, et al. Direct and indirect effects of central and general adiposity on cardiovascular diseases: The Tehran Lipid and Glucose Study. *Eur J Prev Cardiol*. (2018) 25:1170–81. doi: 10.1177/2047487318780030

42. Lu Y, Hajifathalian K, Rimm EB, Ezzati M, Danaei G. Mediators of the effect of body mass index on coronary heart disease: decomposing direct and indirect effects. *Epidemiology*. (2015) 26:153–62. doi: 10.1097/EDE.0000000000000234

43. Li S, Guo B, Chen H, Shi Z, Li Y, Tian Q, et al. The role of the triglyceride (triacylglycerol) glucose index in the development of cardiovascular events: a retrospective cohort analysis. *Sci Rep*. (2019) 9:7320. doi: 10.1038/s41598-019-43776-5

44. Grundy SM. Obesity, metabolic syndrome, and cardiovascular disease. *J Clin Endocrinol Metab*. (2004) 89:2595–600. doi: 10.1210/jc.2004-0372

45. Sinha R, Dufour S, Petersen KF, LeBon V, Enoksson S, Ma YZ, et al. Assessment of skeletal muscle triglyceride content by (1)H nuclear magnetic resonance spectroscopy in lean and obese adolescents: relationships to insulin sensitivity, total body fat, and central adiposity. *Diabetes*. (2002) 51:1022–7. doi: 10.2337/diabetes.51.4.1022

46. Lopez-Jimenez F, Almahmeed W, Bays H, Cuevas A, Di Angelantonio E, le Roux CW, et al. Obesity and cardiovascular disease: mechanistic insights and management strategies. A joint position paper by the World Heart Federation and World Obesity Federation. *Eur J Prev Cardiol*. (2022) 29:2218–37. doi: 10.1093/eurjpc/zwac187

47. Hu G, Tuomilehto J, Silventoinen K, Sarti C, Mannisto S, Jousilahti P. Body mass index, waist circumference, and waist-hip ratio on the risk of total and type-specific stroke. *Arch Intern Med*. (2007) 167:1420–7. doi: 10.1001/archinte.167.13.1420

48. Basri R, Shaik MM, Alam MK, Mondol MBA, Mohammad QD, Gan SH. Waist to hip ratio, waist to height ratio and body mass index predict stroke risk in a Bangladeshi population. *Int Med J*. (2013) 20:740–3.

49. Irisawa H, Mizushima T. Correlation of body composition and nutritional status with functional recovery in stroke rehabilitation patients. *Nutrients*. (2020) 12:1923. doi: 10.3390/nu12071923

50. Steptoe A, Breeze E, Banks J, Nazroo J. Cohort profile: the English longitudinal study of ageing. *Int J Epidemiol*. (2013) 42:1640–8. doi: 10.1093/ije/dys168

51. Kahn BB, Flier JS. Obesity and insulin resistance. *J Clin Invest*. (2000) 106:473–81. doi: 10.1172/JCI10842

52. Shoelson SE, Herrero L, Naaz A. Obesity, inflammation, and insulin resistance. *Gastroenterology*. (2007) 132:2169–80. doi: 10.1053/j.gastro.2007.03.059

53. Qatanani M, Lazar MA. Mechanisms of obesity-associated insulin resistance: many choices on the menu. *Genes Dev*. (2007) 21:1443–55. doi: 10.1101/gad.1550907

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The non-linear relationship between the visceral adiposity index and the risk of prediabetes and diabetes

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Background: The visceral adiposity index is a valuable tool for assessing visceral fat accumulation. However, its non-linear association with prediabetes and diabetes requires further elucidation. Therefore, we aim to clarify the intricate interplay between the visceral adiposity index and these dysglycemic conditions.

Methods: The National Health and Nutrition Examination Survey database from 1999 to 2018 was utilized to analyze health data from 24,072 participants. A multivariate logistic regression model was employed to evaluate the independent association between the visceral adiposity index and prediabetes and diabetes while considering potential confounding factors. Generalized additive models were used to identify any non-linear relationships by fitting smooth curves. Additionally, a stratified analysis based on different baseline characteristics was conducted, along with an interactive analysis.

Results: After accounting for all relevant variables, individuals in the lowest quartile of the visceral adiposity index had a notably diminished likelihood of progressing to prediabetes and diabetes when compared with those in the other three quartiles. The odds ratios and 95% confidence intervals were as follows: 1.37 (1.23, 1.53), 1.87 (1.65, 2.12), and 2.80 (2.33, 3.37). More importantly, a non-linear association was observed between the visceral adiposity index and prediabetes and diabetes, with a threshold identified at 2.10.

Conclusions: There exists a notable and positive association between the visceral adiposity index and prediabetes and diabetes, displaying non-linear attributes in this evaluation of the relationship. Risk assessment and early prevention strategies targeting the maintenance of low levels of visceral adiposity index may substantially diminish the likelihood of developing prediabetes and diabetes.

KEYWORDS

visceral adiposity index, prediabetes, diabetes, non-linear relationship, NHANES

1 Introduction

The incidence of diabetes, a chronic metabolic disease characterized by hyperglycemia, has been rising in recent decades. Moreover, it has become one of the principal contributors to global mortality and disability, imposing significant medical and economic burdens (1). In 2021 alone, approximately 529 million individuals were affected by diabetes globally, with projections indicating a staggering increase to 1,310 million by 2050 (2). The prediabetic condition signifies a substantial risk for progressing to diabetes, and its importance in public health must not be overlooked (3). Projections indicate that more than 470 million people are expected to be affected by prediabetes by 2030, exhibiting twice the incidence rate compared to diabetes itself (4).

Furthermore, an alarming statistic revealed that approximately 5% to 10% of those with prediabetes will progress to full-blown diabetes annually. This figure escalates to an astonishing 50% after 10 years (4, 5). A strong association was found between prediabetes and heightened risks for stroke, cardiovascular disease, kidney disease, and all-cause mortality (6–9). Additionally, several investigations have shown that individuals in the prediabetic state have the opportunity to reverse the condition and return to normal glucose metabolism before developing diabetes (10). Therefore, efficient management strategies necessitate the early detection of prediabetes along with individualized interventions aimed at reducing the burden imposed by diabetes while preventing associated complications.

Obesity, particularly the accumulation of visceral fat, has been firmly linked to a broad spectrum of metabolic disorders (11). Visceral fat accumulation can stimulate excessive secretion of pro-inflammatory factors and adipokines, exacerbating insulin resistance and abnormal blood glucose levels (12). While magnetic resonance imaging and computed tomography (CT) are the best methods for measuring visceral fat, their application in large-scale population screening is limited by cost, complexity, and potential radiation exposure (13). In 2010, Amato et al. introduced the visceral adiposity index (VAI), a novel way to quantify visceral adiposity using waist circumference (WC), body mass index (BMI), triglyceride (TG) levels, and high-density lipoprotein cholesterol (HDL-C) (14). Studies have shown a strong concordance between VAI and CT measurement of visceral fat, which can better predict the occurrence of glucose and lipid metabolism disorders. Furthermore, VAI exhibited an inverse correlation with insulin sensitivity (14). Compared to conventional indicators of adiposity, VAI exhibits superior predictive performance across diverse populations with chronic diseases, serving as a simple and efficacious tool for assessing visceral fat accumulation and dysfunction (15–17). Additionally, an association between VAI and diabetes has been reported, with VAI potentially acting as an independent predictor of diabetes (18).

However, limited research has considered the diabetic population collectively, leaving the complex associations between VAI and prediabetes and diabetes largely unexplored. Furthermore, few previous studies have involved U.S. populations. Therefore, our objective was to evaluate the connection between VAI and prediabetes and diabetes by analyzing data from the National Health and Nutrition Examination Survey (NHANES), while also exploring any potential non-linear associations.

2 Methods

2.1 Study population

Data from the NHANES, a nationally representative survey of American civilians, was used in this study. The database employs a comprehensive multi-stage complex sampling methodology and incorporates data obtained from questionnaires, physical examinations, and laboratory tests, all of which are publicly accessible. All the participants signed an informed consent form. Furthermore, the study protocol received prior approval from the Institutional Review Board of the National Center for Health Statistics (NCHS).

The study was a cross-sectional study that utilized NHANES data spanning from 1999 to 2018, encompassing a total of 101,316 initial participants across the 10 consecutive survey cycles. Exclusion criteria were patients who did not have a determined prediabetes and diabetes status (n=31,476), who were younger than 18 years (n=12,606), who did not have a calculated VAI (n=32,895), and who had an extreme VAI value (mean ± 3 standard deviations) (n=267). Finally, a total of 24,072 eligible participants were included in the analyses (Figure 1).

2.2 Exposure and outcome variables

The exposure variable in this study was VAI, a trustworthy tool for evaluating visceral fat function (14). The computation formula for VAI is as follows: for men, VAI = [WC (cm)/(39.68 + 1.88 x BMI (kg/m2))] × (TG (mmol/L)/1.03) × (1.31/HDL-C (mmol/L)]; for women, VAI = [WC (cm)/(36.58 + 1.89 x BMI (kg/m2))]×(TG (mmol/L)/0.81)×(1.52/HDL-C (mmol/L)).

Prediabetes and diabetes were included as outcome variables in our study. Prediabetes was determined according to any of the following criteria: diagnosed by a physician or health professional, fasting plasma glucose (FPG) levels ranging from 5.6 to 7 mmol/L, glycosylated hemoglobin (HbA1c) levels ranging from 5.7% to 6.5%, or an FPG value during a 2-hour oral glucose tolerance test (OGTT) ranging from 7.8 mmol/L to 11.0 mmol/L. Diabetes was defined as a self-reported physician diagnosis, HBA1c level greater than 6.5%, FPG level greater than 7 mmol/L, or 2-hour OGTT plasma glucose level greater than 11.1 mmol/L. In this study, combined prediabetes and diabetes were analyzed as an outcome variable.

2.3 Covariates

Age, gender, race, education level, smoking, drinking, economic levels, physical activity, blood pressure, triglyceride, total cholesterol (TC), estimated glomerular filtration rate (eGFR), lipid-lowering

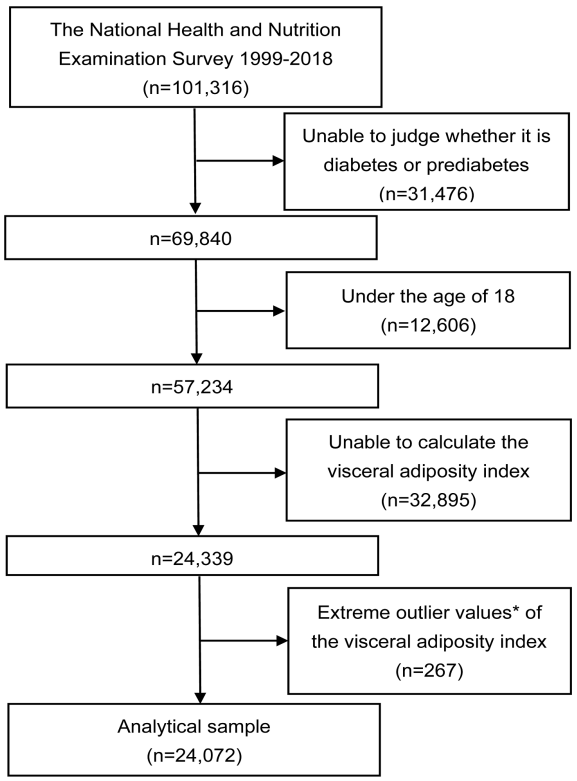

FIGURE 1
Flowchart of the study. *Extreme outlier values were defined as those over 3 standard deviations from the mean.

medications, and antihypertensive medications were included as covariates of no interest into the analyses to correct for error correlations. Among these, race is categorized into non-Hispanic white, non-Hispanic Black, Mexican American, and others. Education level was divided into three groups based on the completion of high school as the distinguishing criterion. Using self-reported data, tobacco smoking status was categorized into three groups: never smokers (smoked <100 cigarettes), former smokers (smoked≥100 cigarettes but had currently quit smoking), and current smokers. We categorized current drinkers according to their alcohol intake as mild drinkers, moderate drinkers, and heavy drinkers. The economic levels were quantified as the poverty-income ratio (PIR), which represents the household income relative to the federal poverty line. These levels were categorized into three groups based on two thresholds: 1.3 and 3.5. The respondents' weekly activity level was evaluated using metabolic equivalents of task (METs). Additionally, eGFR was estimated utilizing the creatinine equation developed by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) in 2009 (19). All variables were collected simultaneously with prediabetes and diabetes prevalence.

2.4 Statistical analysis

The baseline characteristics of the participants were described by VAI quartiles. Continuous variables were expressed as means ± standard deviation and categorical variables as percentages. One-way ANOVA and chi-square tests were used to compare the differences between the four groups. To elucidate the association between VAI and prediabetes and diabetes, we constructed three multiple logistic regression models while adjusting for various covariates. Additionally, a generalized additive model (GAM) was employed to fit the dose-response curve. The characteristics of the fitted smooth curve guided the application of a two-part logistic regression model to investigate potential non-linear associations. A comparison was made between standard and segmented logistic regression models using the log-likelihood ratio test to identify any turning points (considered significant at P<0.05). Moreover, we investigated whether the relationship between VAI and prediabetes and diabetes varied across different subgroups stratified by baseline characteristics such as gender, age, smoking status, alcohol consumption, and hypertension. All data were processed and analyzed using R 3.5.3 and EmpowerStats software, and statistical significance was defined as P < 0.05.

3 Results

3.1 Baseline characteristics of participants

The study enrolled a cohort of 24,072 individuals with an average age of 47.30 ± 19.08 years, among whom 51.43% were female. Table 1 displayed the baseline characteristics of the participants, described based on the quartile distribution of the VAI. Statistically significant differences were noted for all variables except METs/week among the four VAI groups. Compared with the group with lower VAI levels, participants in the highest VAI quartile (Q4) were characterized as older, more women, more non-Hispanic white, lower educational level, more current or former smokers, higher frequency of alcohol consumption, lower PIR, higher blood pressure levels, and lower eGFR. Most notably, the prevalence of prediabetes and diabetes was also higher in those with higher VAI levels.

3.2 Relationship between VAI and prediabetes and diabetes

A multivariate logistic regression analysis was conducted to assess the correlation between VAI and prediabetes and diabetes, as presented in Table 2. The results consistently demonstrated positive associations between continuous VAI values and prediabetes and diabetes across all models, regardless of adjustment for confounding factors. In addition, participants were stratified into quartiles based on their VAI levels, using the first quartile (Q1) as the reference category. We found that with a quarter increase in VAI, there was a significant elevation in the ORs for prediabetes and diabetes, indicating a notable contribution of elevated VAI levels to the prevalence of these conditions (P-value for trend <0.001).

Furthermore, the results obtained by fitting a smooth curve and the two-part logistic regression model suggested that there is also a

10.3389/fendo.2025.1407873

TABLE 1 Baseline characteristics of the participants.

Characteristic	VAI quartiles				P-value
	Q1 (0.09-0.88) N=6018	Q2 (0.88-1.45) N=6018	Q3 (1.45-2.45) N=6018	Q4 (2.45-10.44) N=6018	
Age (years)	42.77 ± 19.29	46.51 ± 19.35	49.47 ± 18.86	50.45 ± 17.86	<0.001
Gender (%)					<0.001
Male	53.79	47.92	46.46	46.10	
Female	46.21	52.08	53.54	53.90	
Race/ethnicity (%)					<0.001
Non-Hispanic white	37.42	42.90	44.52	48.55	
Non-Hispanic Black	32.49	22.93	16.45	10.30	
Mexican American	12.99	16.93	20.99	24.13	
Others	17.10	17.23	18.05	17.02	
Educational level (%)					<0.001
Less than high school	22.91	25.89	29.63	33.63	
High school	22.65	24.13	23.71	24.58	
More than high school	54.44	49.98	46.66	41.80	
Smoking (%)					<0.001
Never	60.09	56.38	53.32	49.15	
Former	21.64	23.88	26.16	27.59	
Now	18.26	19.74	20.52	23.26	
Drinking (%)					<0.001
Never	13.24	14.27	14.31	16.59	
Former	11.95	15.49	19.37	21.96	
Mild	37.20	33.80	32.85	29.94	
Moderate	17.72	15.90	13.50	12.03	
Heavy	19.88	20.54	19.96	19.48	
PIR (%)					<0.001
Low	28.91	29.99	31.32	34.80	
Medium	37.54	37.57	39.72	38.39	
High	33.55	32.44	28.96	26.81	
METs/week (%)					0.097
Low	95.24	94.90	95.55	94.96	
Moderate	2.37	3.02	2.62	3.15	
Vigorous	2.39	2.09	1.83	1.89	
BMI (kg/m^2)	25.61 ± 5.83	27.88 ± 6.37	29.83 ± 6.71	31.01 ± 6.34	<0.001
SBP (mmHg)	119.76 ± 17.98	121.79 ± 18.62	123.84 ± 19.13	125.93 ± 19.39	<0.001
DBP (mmHg)	67.99 ± 11.57	69.06 ± 11.92	69.69 ± 12.24	70.84 ± 12.48	<0.001
TG (mg/dl)	58.38 ± 17.18	89.74 ± 20.56	127.36 ± 29.44	221.50 ± 80.22	<0.001
TC (mg/dl)	179.72 ± 37.10	188.33 ± 39.24	195.78 ± 41.12	207.55 ± 44.55	<0.001
eGFR ($ml/min/1.73\ m^2$)	102.28 ± 23.58	97.60 ± 24.12	94.90 ± 24.61	93.22 ± 25.25	<0.001

(Continued)

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TABLE 1 Continued

Characteristic	VAI quartiles				P-value
	Q1 (0.09-0.88) N=6018	Q2 (0.88-1.45) N=6018	Q3 (1.45-2.45) N=6018	Q4 (2.45-10.44) N=6018	
Lipid-lowering medications (%)	11.06	14.87	19.03	21.49	<0.001
Antihypertensive medications (%)	19.02	25.41	31.73	36.51	<0.001
Glucose metabolism state (%)					<0.001
Normal	61.25	52.18	42.92	33.50	
Prediabetes	30.13	34.53	37.54	38.92	
Diabetes	8.62	13.29	19.54	27.58	

VAI, visceral adiposity index; PIR, poverty income ratio; MET, metabolic equivalent of task; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; TC, total cholesterol; eGFR, estimated glomerular filtration rate.

non-linear association between VAI and prediabetes and diabetes (Table 3, Figure 2). The inflection point was found to be 2.10 after the threshold effect analysis. When the VAI was <2.10, the OR (95% CI) was 2.47 (2.21,2.76); when the VAI> 2.10, the OR (95% CI) was 1.57 (1.46,1.70). This shows that before and after the inflection point, VAI was significantly positively correlated with prediabetes and diabetes. The log-likelihood ratio test showed statistical differences in the slopes between the standard logistic regression model and the piecewise logistic regression model (p<0.001).

3.3 Subgroup analyses

In an effort to ascertain the robustness of the association between VAI and prediabetes and diabetes, we executed stratified subgroup analyses alongside interaction testing (Figure 3). Our findings indicated a maintained positive correlation between VAI and both prediabetes and diabetes across various strata defined by gender, age, smoking habits, alcohol intake, and hypertension. In addition, no significant interaction was reported in all subgroups, indicating that the positive correlation between VAI and prediabetes and diabetes was not related to the above stratification parameters (all p>0.05 for interactions). The stratified analyses revealed that the non-linear correlations of each subgroup were consistent with the overall trend, and there was no significant heterogeneity among different subgroups (Figure 4).

TABLE 2 Relationship between the VAI and prediabetes and diabetes in different models.

VAI	Model 1	Model 2	Model 3
Continuous	1.32 (1.29, 1.34)	1.30 (1.27, 1.32)	1.71 (1.59, 1.85)
Quartiles			
Q1(0.09-0.88)	Reference	Reference	Reference
Q2(0.88-1.45)	1.45 (1.35, 1.56)	1.37 (1.27, 1.49)	1.37 (1.23, 1.53)
Q3(1.45-2.45)	2.10 (1.95, 2.26)	1.89 (1.74, 2.05)	1.87 (1.65, 2.12)
Q4(2.45-10.44)	3.14 (2.91, 3.38)	2.93 (2.69, 3.19)	2.80 (2.33, 3.37)
P for trend	<0.001	<0.001	<0.001

Model 1: Non-adjusted.
Model 2: Adjusted for age, gender, race/ethnicity, and education level.
Model 3: Adjusted for age, gender, race/ethnicity, education level, smoking, drinking, PIR, METs/week, SBP, TG, TC, eGFR, lipid-lowering medications, and antihypertensive medications.
VAI, visceral adiposity index; PIR, poverty income ratio; MET, metabolic equivalent of task; SBP, systolic blood pressure; TG, triglyceride; TC, total cholesterol; eGFR, estimated glomerular filtration rate.

4 Discussion

The purpose of this study was to assess the relationship between the VAI and prediabetes and diabetes among a sample of adult individuals sourced from NHANES data collected from 1999 to 2018. Our results demonstrated a notable positive association between the VAI and both prediabetes and diabetes, which persisted regardless of adjustments for confounding variables. In addition, we found a non-linear relationship between the VAI and both prediabetes and diabetes and determined an inflection point of 2.10 for the VAI level. When the population was stratified by gender, age, smoking, drinking, and hypertension, the results were consistent with the overall population, and no effect modifiers were detected that influenced the changes in the association of the VAI with prediabetes and diabetes. These findings supported the potential utility of VAI as a predictive tool for recognizing individuals susceptible to prediabetes and diabetes in an early stage.

The association of the VAI, as an index innovatively devised to gauge visceral adiposity function, with diabetes has been established in many previous studies (18, 20). A meta-analysis reported a significant positive correlation between the VAI and diabetes, which emphasizes the potential role of the VAI in the development of diabetes (18). Similarly, an aggregated examination of 216 longitudinal studies demonstrated that every unit increase in the VAI is associated with a 42% increase in the likelihood of developing diabetes (21). A study in the Chinese population showed that compared with TG, HDL-C, and other indicators, the VAI had obvious advantages in predicting diabetes in normoglycemic subjects (22).

10.3389/fendo.2025.1407873

TABLE 3 Threshold effect analysis of the VAI on prediabetes and diabetes using a two-part logistic regression model.

VAI	Adjusted OR* (95% CI)	P-value
Model I		
Fitting by the standard linear model	1.71 (1.59, 1.85)	<0.0001
Model II		
Inflection point	2.10	
< Inflection point	2.47 (2.21, 2.76)	<0.0001
> Inflection point	1.57 (1.46, 1.70)	<0.0001
Log likelihood ratio	/	<0.001

*Adjusted for age, gender, race/ethnicity, education level, smoking, drinking, PIR, METs/week, SBP, TG, TC, eGFR, lipid-lowering medications, and antihypertensive medications. VAI, visceral adiposity index; OR, odd ratio; CI, confidence interval.; PIR, poverty income ratio; MET, metabolic equivalent of task; SBP, systolic blood pressure; TG, triglyceride; TC, total cholesterol; eGFR, estimated glomerular filtration rate.

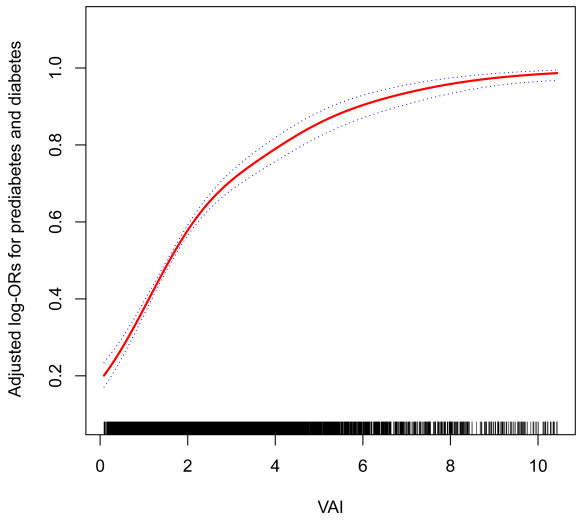

FIGURE 2
The non-linear association between the VAI and the prevalence of prediabetes and diabetes. Age, gender, race/ethnicity, education level, smoking, drinking, PIR, METs/week, SBP, TG, TC, eGFR, lipid-lowering medications, and antihypertensive medications were adjusted for. VAI, visceral adiposity index; PIR, poverty income ratio; MET, metabolic equivalent of task; SBP, systolic blood pressure; TG, triglyceride; TC, total cholesterol; eGFR, estimated glomerular filtration rate.

There are a large number of people in the prediabetic state, and many patients may even be undetected. If not taken seriously, they may progress to diabetes and have an increased risk of developing many chronic diseases. Therefore, we included the prediabetic population in this study, together with diabetes as an outcome variable, to evaluate their association with the VAI. We found that subjects in the uppermost quarter of VAI had a 2.8 times increased likelihood of prediabetes and diabetes compared to those in the lowest quarter. A study of the Chinese population supports our findings (23). Similarly, a meta-analysis of 112,603 participants showed that VAI might increase the risk for prediabetes (24). In addition, in the German population study, VAI was also found to have high sensitivity for the identification of both prediabetes and diabetes, and its ability to distinguish abnormal blood glucose was comparable to that of HOMA-IR, an established marker for the diagnosis of insulin resistance (25). In addition, our subgroup analyses showed that the association of the VAI with prediabetes and diabetes was independent of factors such as age, gender, smoking, alcohol consumption, and hypertension. This suggests that the VAI may be a potential independent risk indicator for prediabetes and diabetes.

The presence of excessive abdominal fat is linked to an increased likelihood of insulin resistance and impaired β-cell function (26). The VAI, a proxy for cardiometabolic risk in healthy individuals, has shown a significant inverse correlation with insulin sensitivity (14). The biological pathways through which heightened VAI levels contribute to the augmented risk of prediabetes and diabetes potentially involve impacts on insulin resistance, pancreatic β-cell function, and adiponectin levels (27). Adipose tissue is known to release multiple pro-inflammatory factors and adipokines, fostering a chronic inflammatory state that can induce β-cell damage and exacerbate insulin resistance, eventually leading to diabetes (28, 29). Secondly, a high level of free fatty acids in individuals with obesity increases TG storage in the muscle and liver, reduces insulin sensitivity, and causes lipotoxic responses (30, 31). In addition, studies have shown that the VAI is the only determinant of adiponectin levels and can play an indirect role in impaired adiponectin levels and glucose metabolism (32, 33).

It is noteworthy that the relationship between the VAI and prediabetes and diabetes also exhibited a non-linear pattern. However, the results of previous studies are still controversial. A study was consistent with our results in patients with hypertension (34). Furthermore, a dose-response meta-analysis of longitudinal studies also revealed a monotonic positive association between the VAI and the risk of diabetes (21). In contrast, the study by Fang et al. stated that no non-linear relationship was detected between the VAI and diabetes (18). This disparity could stem from variations in participant selection criteria or might be ascribed to dissimilarities in the research methodologies and designs employed. In our study, we observed a significant non-linear relationship between the VAI and the prevalence of prediabetes and diabetes, which showed a parabolic curve trend. Specifically, the risk of prediabetes and diabetes increased significantly with increasing VAI values. However, after the VAI values exceeded a specific threshold of 2.10, the rate of increase plateaued, although the risk remained high. The explanations for these results may be as follows: first, excessive accumulation of visceral fat may adversely affect metabolic processes such as insulin sensitivity and inflammatory response, thereby increasing the risk of diabetes. However, when visceral fat accumulates to a certain extent, the increased risk may no longer follow a simple linear pattern due to limitations in biological mechanisms or individual metabolic differences. In addition, we need to consider possible biases in study design and data collection. A significant proportion of overweight individuals or individuals with obesity may have been excluded from the study due to death, serious illness, or other reasons that precluded participation in the interview. Nonetheless, the identification of the VAI inflection point provides a reference value for clinicians to

10.3389/fendo.2025.1407873

Characteristics	OR (95% CI)	P-value	P-interaction*
Gender			0.55
Male	1.69 (1.54, 1.85)	< 0.05	
Female	1.72 (1.59, 1.86)	< 0.05	
Age (years)			0.33
<45	1.69 (1.57, 1.83)	< 0.05	
45-60	1.68 (1.53, 1.84)	< 0.05	
≥60	1.78 (1.62, 1.96)	< 0.05	
Smoking			0.10
Never	1.72 (1.58, 1.86)	< 0.05	
Former	1.81 (1.65, 1.99)	< 0.05	
Now	1.67 (1.53, 1.82)	< 0.05	
Drinking			0.84
Never	1.67 (1.51, 1.84)	< 0.05	
Former	1.71 (1.56, 1.88)	< 0.05	
Mild	1.71 (1.57, 1.87)	< 0.05	
Moderate	1.74 (1.58, 1.93)	< 0.05	
Heavy	1.76 (1.60, 1.93)	< 0.05	
Hypertension			0.49
Yes	1.75 (1.60, 1.90)	< 0.05	
No	1.71 (1.58, 1.85)	< 0.05	

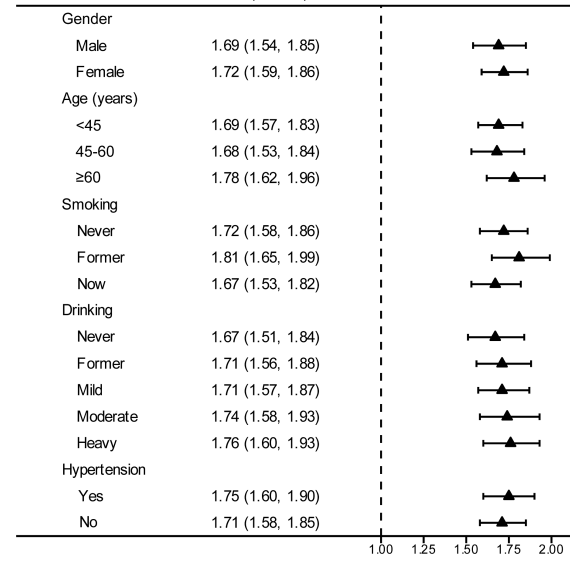

FIGURE 3
Stratified analyses between the VAI and the prevalence of prediabetes and diabetes. *Each stratification adjusted for all the factors (age, gender, race/ethnicity, education level, smoking, drinking, PIR, METs/week, SBP, TG, TC, eGFR, lipid-lowering medications, and antihypertensive medications) except the stratification factor itself. OR, odd ratio; CI, confidence interval; VAI, visceral adiposity index; PIR, poverty income ratio; MET, metabolic equivalent of task; SBP, systolic blood pressure; TG, triglyceride; TC, total cholesterol; eGFR, estimated glomerular filtration rate.

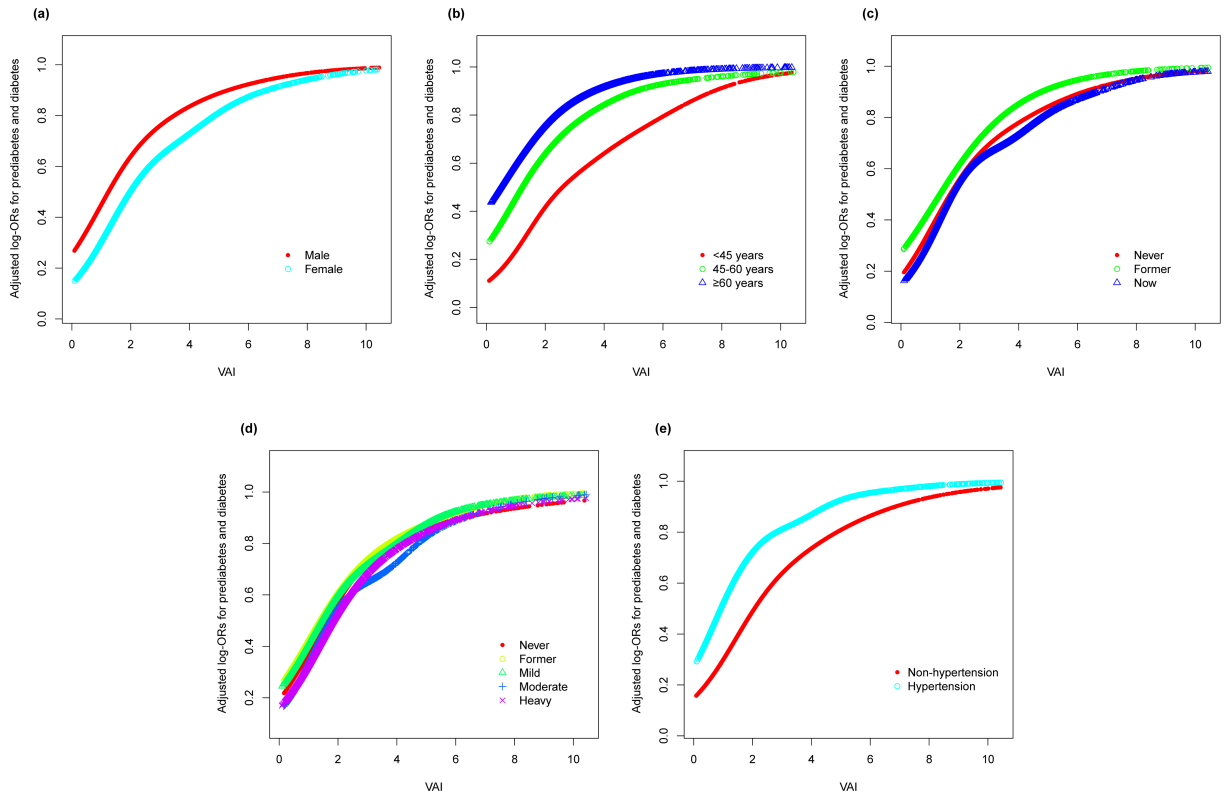

FIGURE 4
Stratified analyses (by **(a)** gender; **(b)** age; **(c)** smoking; **(d)** drinking; **(e)** hypertension) between VAI and the prevalence of prediabetes and diabetes using generalized additive model and smooth curve fittings. *Each generalized additive model and smooth curve fitting was adjusted for all factors, including age, gender, race/ethnicity, education level, smoking, drinking, PIR, METs/week, SBP, TG, TC, eGFR, lipid lowering medications, and antihypertensive medications, except for the stratification factor itself. VAI, visceral adiposity index; PIR, poverty income ratio; MET, metabolic equivalent of task; SBP, systolic blood pressure; TG, triglyceride; TC, total cholesterol; eGFR, estimated glomerular filtration rate.

assess an individual's risk of developing prediabetes or diabetes more accurately. At the same time, this finding also highlights the need for further research on the VAI and its complex relationship with prediabetes and diabetes risk.

Nonetheless, the research has certain limitations. First, it should be noted that the study relies exclusively on a cross-sectional methodology, which ultimately obstructs the determination of a causal connection regarding the relationship between the VAI and prediabetes and diabetes. Consequently, further extensive prospective studies are required to validate these findings. Second, it is important to acknowledge that the dataset employed for this study originated from the NHANES database, which may restrict its generalizability across diverse ethnicities and populations. Moreover, a considerable number of participants who lacked essential data for VAI calculation were excluded from the analysis. Finally, despite our consideration of various potential effect modifiers, there remains a possibility of unidentified confounders leading to selection bias. Therefore, cautious interpretation is warranted when considering the outcomes derived from this investigation.

5 Conclusions

This cross-sectional study, utilizing the NHANES database, has substantiated a non-linear positive association between the VAI and prediabetes and diabetes. These findings suggest that the VAI has potential as a biomarker for predicting the onset of prediabetes and diabetes, offering novel perspectives for risk evaluation and preventive healthcare approaches. Nevertheless, further prospective cohort studies are warranted to validate these observations.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: https://www.cdc.gov/nchs/nhanes/index.htm.

Ethics statement

The studies involving humans were approved by the Institutional Review Board of the National Center for Health Statistics. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

LH: Conceptualization, Data curation, Formal Analysis, Methodology, Software, Validation, Visualization, Writing – original draft. JL: Funding acquisition, Project administration, Resources, Supervision, Writing – review & editing. CL: Methodology, Project administration, Supervision, Writing – review & editing. YY: Funding acquisition, Project administration, Resources, Supervision, Writing – review & editing. YM: Formal Analysis, Methodology, Validation, Writing – review & editing. YW: Conceptualization, Data curation, Project administration, Resources, Software, Supervision, Validation, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Bommer C, Heesemann E, Sagalova V, Manne-Goehler J, Atun R, Bärnighausen T, et al. The global economic burden of diabetes in adults aged 20-79 years: A cost-of-illness study. *Lancet Diabetes Endocrinol.* (2017) 5:423–30. doi: 10.1016/s2213-8587(17)30097-9

2. GBD 2021 Diabetes Collaborators. Global, regional, and national burden of diabetes from 1990 to 2021, with projections of prevalence to 2050: A systematic analysis for the global burden of disease study 2021. *Lancet.* (2023) 402:203–34. doi: 10.1016/s0140-6736(23)01301-6

3. Jin J. What is prediabetes? *Jama.* (2023) 330:2404. doi: 10.1001/jama.2023.17846

4. Tabák AG, Herder C, Rathmann W, Brunner EJ, Kivimäki M. Prediabetes: A high-risk state for diabetes development. *Lancet.* (2012) 379:2279–90. doi: 10.1016/s0140-6736(12)60283-9

5. Morris DH, Khunti K, Achana F, Srinivasan B, Gray LJ, Davies MJ, et al. Progression rates from hba1c 6.0-6.4% and other prediabetes definitions to type 2 diabetes: A meta-analysis. *Diabetologia.* (2013) 56:1489–93. doi: 10.1007/s00125-013-2902-4

6. Echouffo-Tcheugui JB, Perreault L, Ji L, Dagogo-Jack S. Diagnosis and management of prediabetes: A review. *Jama.* (2023) 329:1206–16. doi: 10.1001/jama.2023.4063

7. Ali MK, Bullard KM, Saydah S, Imperatore G, Gregg EW. Cardiovascular and renal burdens of prediabetes in the USA: analysis of data from serial cross-sectional surveys, 1988-2014. *Lancet Diabetes Endocrinol*. (2018) 6:392–403. doi: 10.1016/s2213-8587(18)30027-5

8. Huang Y, Cai X, Mai W, Li M, Hu Y. Association between prediabetes and risk of cardiovascular disease and all cause mortality: systematic review and meta-analysis. *Bmj*. (2016) 355:i5953. doi: 10.1136/bmj.i5953

9. Gujral UP, Jagannathan R, He S, Huang M, Staimez LR, Wei J, et al. Association between varying cut-points of intermediate hyperglycemia and risk of mortality, cardiovascular events and chronic kidney disease: A systematic review and meta-analysis. *BMJ Open Diabetes Res Care*. (2021) 9(1):e001776. doi: 10.1136/bmjdrc-2020-001776

10. Galaviz KI, Weber MB, Suvada KB, Gujral UP, Wei J, Merchant R, et al. Interventions for reversing prediabetes: A systematic review and meta-analysis. *Am J Prev Med*. (2022) 62:614–25. doi: 10.1016/j.amepre.2021.10.020

11. Karlsson T, Rask-Andersen M, Pan G, Höglund J, Wadelius C, Ek WE, et al. Contribution of genetics to visceral adiposity and its relation to cardiovascular and metabolic disease. *Nat Med*. (2019) 25:1390–5. doi: 10.1038/s41591-019-0563-7

12. Bensussen A, Torres-Magallanes JA, Roces-de-Álvarez-Buylla E. Molecular tracking of insulin resistance and inflammation development on visceral adipose tissue. *Front Immunol*. (2023) 14:1014778. doi: 10.3389/fimmu.2023.1014778

13. Fang H, Berg E, Cheng X, Shen W. How to best assess abdominal obesity. *Curr Opin Clin Nutr Metab Care*. (2018) 21:360–5. doi: 10.1097/mco.0000000000000485

14. Amato MC, Giordano C, Galia M, Criscimanna A, Vitabile S, Midiri M, et al. Visceral adiposity index: A reliable indicator of visceral fat function associated with cardiometabolic risk. *Diabetes Care*. (2010) 33:920–2. doi: 10.2337/dc09-1825

15. Wei J, Liu X, Xue H, Wang Y, Shi Z. Comparisons of visceral adiposity index, body shape index, body mass index and waist circumference and their associations with diabetes mellitus in adults. *Nutrients*. (2019) 11(7):1580. doi: 10.3390/nu11071580

16. Jabłonowska-Lietz B, Wrzosek M, Włodarczyk M, Nowicka G. New indexes of body fat distribution, visceral adiposity index, body adiposity index, waist-to-height ratio, and metabolic disturbances in the obese. *Kardiol Pol*. (2017) 75:1185–91. doi: 10.5603/KP.a2017.0149

17. Bijari M, Jangjoo S, Emami N, Raji S, Mottaghi M, Moallem R, et al. The accuracy of visceral adiposity index for the screening of metabolic syndrome: A systematic review and meta-analysis. *Int J Endocrinol*. (2021) 2021:6684627. doi: 10.1155/2021/6684627

18. Shen F, Guo C, Zhang D, Liu Y, Zhang P. Visceral adiposity index as a predictor of type 2 diabetes mellitus risk: A systematic review and dose-response meta-analysis. *Nutr Metab Cardiovasc Dis*. (2023) 34(4):811–22. doi: 10.1016/j.numecd.2023.04.009

19. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. (2009) 150:604–12. doi: 10.7326/0003-4819-150-9-200905050-00006

20. Nusrianto R, Tahapary DL, Soewondo P. Visceral adiposity index as a predictor for type 2 diabetes mellitus in asian population: A systematic review. *Diabetes Metab Syndr*. (2019) 13:1231–5. doi: 10.1016/j.dsx.2019.01.056

21. Jayedi A, Soltani S, Motlagh SZ, Emadi A, Shahinfar H, Moosavi H, et al. Anthropometric and adiposity indicators and risk of type 2 diabetes: systematic review and dose-response meta-analysis of cohort studies. *Bmj*. (2022) 376:e067516. doi: 10.1136/bmj-2021-067516

22. Wang B, Zhang M, Liu Y, Sun X, Zhang L, Wang C, et al. Utility of three novel insulin resistance-related lipid indices for predicting type 2 diabetes mellitus among people with normal fasting glucose in rural China. *J Diabetes*. (2018) 10:641–52. doi: 10.1111/1753-0407.12642

23. Liu PJ, Ma F, Lou HP, Chen Y. Visceral adiposity index is associated with pre-diabetes and type 2 diabetes mellitus in chinese adults aged 20-50. *Ann Nutr Metab*. (2016) 68:235–43. doi: 10.1159/000446121

24. Wang D, Fang R, Han H, Zhang J, Chen K, Fu X, et al. Association between visceral adiposity index and risk of prediabetes: A meta-analysis of observational studies. *J Diabetes Investig*. (2022) 13:543–51. doi: 10.1111/jdi.13685

25. Ahn N, Baumeister SE, Amann U, Rathmann W, Peters A, Huth C, et al. Visceral adiposity index (Vai), lipid accumulation product (Lap), and product of triglycerides and glucose (Tyg) to discriminate prediabetes and diabetes. *Sci Rep*. (2019) 9:9693. doi: 10.1038/s41598-019-46187-8

26. Moon HU, Ha KH, Han SJ, Kim HJ, Kim DJ. The association of adiponectin and visceral fat with insulin resistance and B-cell dysfunction. *J Korean Med Sci*. (2019) 34: e7. doi: 10.3346/jkms.2019.34.e7

27. Qin Y, Qiao Y, Wang D, Li M, Yang Z, Li L, et al. Visceral adiposity index is positively associated with fasting plasma glucose: A cross-sectional study from national health and nutrition examination survey 2017-2020. *BMC Public Health*. (2023) 23:313. doi: 10.1186/s12889-023-15231-8

28. Fontana L, Eagon JC, Trujillo ME, Scherer PE, Klein S. Visceral fat adipokine secretion is associated with systemic inflammation in obese humans. *Diabetes*. (2007) 56:1010–3. doi: 10.2337/db06-1656

29. Kahn SE, Hull RL, Utzschneider KM. Mechanisms linking obesity to insulin resistance and type 2 diabetes. *Nature*. (2006) 444:840–6. doi: 10.1038/nature05482

30. Sachs S, Zarini S, Kahn DE, Harrison KA, Perreault L, Phang T, et al. Intermuscular adipose tissue directly modulates skeletal muscle insulin sensitivity in humans. *Am J Physiol Endocrinol Metab*. (2019) 316:E866–e79. doi: 10.1152/ajpendo.00243.2018

31. Papaetis GS, Papakyriakou P, Panagiotou TN. Central obesity, type 2 diabetes and insulin: exploring a pathway full of thorns. *Arch Med Sci*. (2015) 11:463–82. doi: 10.5114/aoms.2015.52350

32. Al-Daghri NM, Al-Attas OS, Alokail MS, Alkharfy KM, Charalampidis P, Livadas S, et al. Visceral adiposity index is highly associated with adiponectin values and glycaemic disturbances. *Eur J Clin Invest*. (2013) 43:183–9. doi: 10.1111/eci.12030

33. Orrù S, Nigro E, Mandola A, Alfieri A, Buono P, Daniele A, et al. A functional interplay between igf-1 and adiponectin. *Int J Mol Sci*. (2017) 18(10):2145. doi: 10.3390/ijms18102145

34. Deng H, Hu P, Li H, Zhou H, Wu X, Yuan M, et al. Novel lipid indicators and the risk of type 2 diabetes mellitus among chinese hypertensive patients: findings from the guangzhou heart study. *Cardiovasc Diabetol*. (2022) 21:212. doi: 10.1186/s12933-022-01660-z

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