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Surrogate Biomarker to Identify Obesity and Predict Cardiovascular Disease Risk: A Systematic Review

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ABSTRACT
This study investigates the relationship between obesity and cardiovascular disease (CVD) risk by comparing the use of body mass index (BMI) versus other biomarkers in predicting CVD risk among obese individuals. It conducts a systematic literature review following the PRISMA guidelines, searching databases for relevant articles published from 2017-2022. The review analyzes 12 eligible articles and finds that factors beyond just BMI, such as genetics, physical activity, metabolic disorders, previous heart disease history, nutrition, fat distribution, and changes in BMI, can significantly impact the prognosis of heart disease in obese individuals. Importantly, the study shows that measures of fat distribution like waist-to-height ratio, waist circumference, log-transformed body shape index (LBSIZ), and the ratio of visceral adipose tissue (VAT) to subcutaneous adipose tissue (SAT) are superior to BMI in predicting CVD risk among those with obesity. The key takeaway is that while obesity is strongly linked to CVD risk, BMI alone often fails to predict that risk accurately. Fat distribution measures may be a more effective tool for identifying obesity status and predicting associated CVD risk compared to relying solely on BMI. The findings imply that future research should further explore these alternative biomarkers, and clinical practice may benefit from incorporating them into risk assessment protocols. Explicitly stating the significance or impact of these findings strengthens the abstract and highlights the potential implications for future research and clinical practice.

Keywords: Body Mass Indeks, Biomarkers, Cohort, Cardiovascular Disease, Obesity, Fat Distribution, Risk Assessment.

INTRODUCTION

Cardiovascular disease (CVD) poses a significant global public health challenge and stands as the leading cause of death worldwide. Over the last decade, CVD-related deaths have risen notably, escalating from 12.1 million to 18.6 million. In Indonesia, CVD represents a critical area of focus for the Ministry of Health as part of efforts to reform the healthcare system, particularly in enhancing referral services. The prevalence of CVD among Indonesians continues to increase, resulting in heightened levels of illness, disability, and socioeconomic burdens affecting individuals, families, communities, and the nation at large. According to Indonesia's Sample Registration System (SRS),

cardiovascular disease (CVD) ranks as the second most common cause of death in the country following stroke, comprising 12.9% of all leading causes of mortality. This underscores the escalating public health challenge posed by CVD, both on a global scale and within Indonesia. It emphasizes CVD's significance as a focal point for healthcare system improvements and acknowledges its substantial impact on mortality rates and socioeconomic burdens in the country (Bahruddin et al., 2024; Hikmayani & Rachmawan, 2024; Lawton et al., 2024; Luh Putu Maitra Agastya et al., 2024; Mboi et al., 2022; Organization, 2022; Roth et al., 2020; Sibarani et al., 2022; Utama et al., 2024).

Obesity is strongly associated with diabetes, hypertension, and other metabolic disorders, all of which contribute to an increased risk of cardiovascular disease (CVD). This has led to a widespread global health crisis, with obesity rates experiencing significant growth over the past 35 years. Current estimates indicate that approximately 39% to 49% of the worldwide population, equivalent to 2.8-3.5 billion people, are affected by obesity. In Indonesia, the prevalence of central obesity has notably increased from 18.8% in 2007 to 31% in 2018, highlighting a concerning upward trend. These trends underscore the critical role of obesity in escalating CVD risk on a global scale (Anyanwu et al., 2022; Martantiningtyas et al., 2021; Organization, 2022; Ren et al., 2022).

Cardiovascular disease (CVD) comprises various disorders that impact the heart, blood vessels, or both. This category includes conditions like coronary heart disease (CHD), cerebrovascular disease, rheumatic heart disease, congenital heart disease, deep vein thrombosis, and pulmonary embolism. CVD generally arises from a combination of multiple risk factors rather than a singular cause. Effective management and prevention of these risk factors can play a crucial role in controlling and preventing cardiovascular diseases (Birarra et al., 2022).

Obesity or overweight refers to a condition where an individual's weight significantly exceeds the normal range, stemming from an imbalance between energy intake and expenditure. According to the World Health Organization (WHO), being overweight is characterized by a body mass index (BMI) of 25 to 30 kg/m², while obesity is defined by a BMI exceeding 30 kg/m². However, abdominal obesity can manifest independently of overall obesity as defined by BMI. This condition, termed "normal weight obesity," can lead to the misclassification and underdiagnosis of cardiovascular and cardiometabolic diseases. It primarily affects individuals with excess abdominal fat who do not meet the standard BMI criteria for obesity (Ren et al., 2022).

Despite numerous studies confirming a link between obesity and cardiovascular disease (CVD), ongoing discussions persist regarding the underlying mechanisms driving this association. Intriguingly, some research has identified a paradoxical phenomenon wherein specific subgroups exhibit lower mortality rates among individuals who are overweight or obese. This suggests that the relationship between obesity and mortality from CVD may not be straightforward and could be influenced by factors such as age, ethnicity, or concurrent health conditions. Further research is essential to comprehensively grasp these intricate dynamics and their implications for public health strategies aimed at preventing cardiovascular diseases (Riaz et al., 2018).

Due to the ongoing debate, it is crucial to conduct a systematic review of the literature to thoroughly investigate the relationship between obesity and cardiovascular

disease (CVD). Presently, there seems to be a shortage of studies or literature reviews, especially in Indonesia, that specifically examine this connection. Therefore, we conducted a systematic literature review to identify, evaluate, and analyze existing research to ascertain the presence and extent of the association between obesity and CVD. This review seeks to offer a comprehensive understanding of the current state of research in this area, highlighting any discrepancies or knowledge gaps in the findings.

RESEARCH METHODS

This systematic literature review adheres to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) methodology, which encompasses four main stages: identification, screening, eligibility, and inclusion of pertinent studies. A comprehensive search was conducted using electronic databases like PubMed, ScienceDirect, and Sage Journals to retrieve relevant journal articles. The review encompasses various study types, with a particular focus on cohort studies aimed at exploring the correlation between obesity and cardiovascular disease. This approach is designed to systematically collect, assess, and synthesize available evidence from the literature, ensuring a rigorous evaluation of the relationship between obesity and CVD (Page et al., 2021).

The inclusion criteria at the beginning of the search in the database were English-language journals, articles with full-text open access, publication time with the range of 2017 – 2022, respondents of all ages and genders in the field of public health and cardiology, and journals that discuss risk factors for obesity with cardiovascular disease. Meanwhile, the exclusion criteria include literature in the form of non-journals, systematic reviews, and duplicate titles that will be issued in this study, journals or articles that discuss cardiovascular risk factors other than obesity (Page et al., 2021).

RESULTS AND DISCUSSION

Following the initial literature search using keywords such as obesity, cohort, and cardiovascular disease, a meticulous screening process was conducted based on pre-defined inclusion criteria and the publication timeframe from 2017 to 2022. This screening yielded a total of 12 suitable pieces of literature that met the criteria for further detailed review and analysis. These selected studies will now undergo a thorough evaluation to assess the relationship between obesity and cardiovascular disease, as reported in the literature during the specified period.

Table 1. Results of Literature Study

No.	Writer	Research Results
1.	Honda et al, (2022)	Over the course of the 5-year study, the 2,140 participants showed an average weight loss of 1.6%. Among them, 496 individuals (23.2%) maintained their obesity status, while 103 participants (4.8%) shifted from being obese to non-obese. Furthermore, the majority, 1,462 participants (68.3%), remained non-obese throughout the study period, while 78 participants (3.6%) transitioned from non-obese to obese. Both groups that experienced changes in obesity status—transitioning from obese to non-obese and from non-obese to

		obese—showed elevated risks of cardiovascular disease (CVD). The group that shifted from obese to non-obese exhibited the smallest increase in CVD risk, with predictions rising from 5.9% to 6.9% in 2007, a statistically significant finding ($P < 0.01$). Conversely, the non-obese-to-obese group showed the largest increase in CVD risk prediction, increasing from 5.7% to 8.2% in 2007, which was also statistically significant ($P < 0.08$). These findings underscore the impact of changes in obesity status on cardiovascular health outcomes. Additional investigation uncovered a relationship between changes in body weight percentage and shifts in cardiovascular disease (CVD) risk indicators. Notably, weight gain was significantly associated with rises in waist circumference, blood pressure levels, fasting blood sugar levels, hemoglobin concentrations, and cholesterol levels, while also correlating with a decline in serum HDL cholesterol levels over the course of the research period. These results underscore the influence of body weight fluctuations on multiple factors that contribute to increased risk of cardiovascular disease.
2.	Lee et al, (2021)	Over a decade-long study involving 1,015 participants, averaging 56.4 years in age and predominantly male, 37.5% developed Coronary Artery Calcification (CAC). Key contributors to CAC included a body mass index (BMI) of ≥25 kg/m^2, increased waist circumference, and a high ratio of visceral adipose tissue to subcutaneous tissue. Notably, individuals with a visceral adipose tissue dominance of ≥30% exhibited a significantly heightened risk of CAC development, indicated by a hazard ratio of 2.20 and a statistically significant P-value of less than 0.001. This highlights the independent predictive capability of visceral fat levels in assessing the risk of CAC, regardless of changes in BMI and waist circumference..
3.	Oh et al, (2020)	Participants in the study were categorized according to their body shape using the z-score of the log-transformed body shape index (LBSIZ) into four distinct groups. These groups included metabolically healthy non-obese (MHNO), which acted as the reference category, as well as metabolically healthy obese (MHO), metabolically unhealthy non-obese (MUNO), and metabolically unhealthy obese (MUO). This classification enabled a thorough examination of how different body shapes and metabolic statuses correlate with health outcomes among the study participants.

		During the 12-year study period from 2001 to 2012, the incidence rate of cardiovascular disease (CVD) was 8.53 cases per 1,000 person-years. Analysis of the data revealed varying hazard ratios (HR) for CVD events among different groups: the metabolically unhealthy obese (MUO) group exhibited the highest HR of 1.82 (95% CI 1.45-2.27), followed by the metabolically unhealthy non-obese (MUNO) group with an HR of 1.46 (95% CI 1.15-1.85), and the metabolically healthy obese (MHO) group with an HR of 1.29 (95% CI 0.96-1.73). These HRs were compared to the reference group of metabolically healthy non-obese (MHNO) individuals. Furthermore, individuals categorized in the metabolically healthy obese (MHO) group showed an increased risk of cardiovascular disease (CVD) events, particularly those in the third trimester with a hazard ratio (HR) of 2.40 (95% CI 1.28-4.51). This risk escalated further in the fourth trimester, where the HR elevated to 3.67 (95% CI 1.99-6.74), compared to participants classified in the metabolically healthy non-obese (MHNO) group. These findings highlight the diverse risks associated with both metabolic health and obesity status in relation to cardiovascular outcomes observed over the course of the study.
4.	Polemiti et al, (2021)	In this study, macrovascular events were defined as occurrences of myocardial infarction and stroke, whereas microvascular events encompassed kidney disease, retinopathy, and neuropathy. Body mass index (BMI) classifications were categorized according to World Health Organization (WHO) guidelines: normal (18.5–24.9 kg/m²), overweight (25.0–29.9 kg/m²), obese I (30.0–34.9 kg/m²), and obese II (≥35.0 kg/m²). Changes in BMI were classified as increased BMI (>1% gain), stable BMI (≤1% gain/loss), and decreased BMI (>1% loss). These criteria were employed to investigate the relationship between BMI fluctuations and the incidence of both macrovascular and microvascular events within the study population. Over an average follow-up period of 10.8 years, the study recorded 85 macrovascular events, such as myocardial infarction and stroke, and 347 microvascular events, including kidney disease, neuropathy, and retinopathy. The analysis did not find any clear link between BMI measured prior to the diagnosis of diabetes mellitus (DM) and changes in BMI concerning the occurrence of macrovascular events. Higher body mass index (BMI) before diabetes diagnosis was found to be significantly associated with an increased risk

		of microvascular complications. Specifically, for every 5 kg/m² increase in BMI, the hazard ratio for microvascular complications was 1.21 (95% CI: 1.07-1.36). This association was particularly strong for kidney disease, with a hazard ratio of 1.39 (95% CI: 1.21-1.60), and less pronounced for neuropathy, with a hazard ratio of 1.12 (95% CI: 0.96-1.31). These findings highlight the impact of higher BMI levels before diabetes onset on the risk of developing microvascular complications among study participants. The analysis of BMI changes revealed that a reduction in BMI greater than 1% was associated with a decreased risk of microvascular complications. Specifically, this reduction in BMI was linked to a lower risk of kidney disease (HR 0.57; 95% CI: 0.40-0.81) and showed a trend towards reduced risk of neuropathy (HR 0.73; 95% CI: 0.52-1.03), compared to individuals whose BMI remained stable. In contrast, there was no clear association found between BMI changes and macrovascular complications, with an HR of 1.04 (95% CI: 0.62-1.74). These findings highlight the potential benefit of BMI reduction in mitigating the risk of microvascular complications among individuals studied, underscoring the importance of weight management in diabetes care.
5	Chien et al, (2021)	The ASIAN-HF study, which involved 5,964 participants with a mean age of 60.8 years and a diagnosis of heart failure, examined the relationship between body mass index (BMI) and waist-to-height ratio (WHtR) with heart failure outcomes. The study found that a high WHtR was associated with a significant increase in body fat percentage (0.38%) and increased the risk of heart failure events, regardless of whether the ejection fraction was reduced (HFrEF) or preserved (HFpEF). Notably, individuals with a high WHtR and lower BMI (< 24.5 kg/m²) had a higher hazard ratio (HR) of 1.93 (95% CI 1.17-3.18; P-value 0.010) for these events compared to those with obesity. This suggests that WHtR is a more significant predictor of adverse outcomes in heart failure, regardless of BMI status. These findings highlight the importance of considering WHtR in addition to BMI when assessing heart failure risk and managing patients with heart failure The study found that individuals classified as underweight, particularly those with a high Waist-to-Height Ratio (WHtR), had a significantly higher risk of death during hospitalization for heart failure. The Hazard Ratio (HR) for this group was 2.01 (95% CI 1.11–3.65, p = 0.022). Additionally, the

		study observed a notable increase in cardiovascular disease (CVD) mortality among underweight individuals compared to those who were obese, with a statistically significant p-value of 0.026. These findings emphasize the heightened risks associated with being underweight in the context of heart failure and cardiovascular outcomes. The study found that individuals with a lower BMI (< 24.5 kg/m²) and higher Waist-to-Height Ratio (WHtR) (≥ 0.55) had a significantly increased risk of developing composite heart failure. This association was consistent across different types of heart failure, including Heart Failure with Preserved Ejection Fraction (HFpEF) and Heart Failure with Reduced Ejection Fraction (HFrEF). Specifically, the Hazard Ratio (HR) for this group was 1.93 (95% CI 1.17 to 3.18, p = 0.01). This highlights the importance of considering both BMI and WHtR in assessing heart failure risk and managing patients with heart failure.
6	Kaltoft et al, (2020)	A comprehensive study spanning 8.7 years and involving 108,304 participants found a significant correlation between genetically elevated body mass index (BMI) and increased risks associated with aortic valve stenosis and the need for valve replacement surgery. Specifically, each 1 kg/m² increase in BMI was linked to a 52% higher relative risk (RR) of developing aortic valve stenosis (95% CI: 1.23 - 1.87) and a 49% higher RR of requiring aortic valve replacement surgery (95% CI: 1.07 - 2.05). Additionally, hazard ratios (HR) indicated a 6% increased risk (HR 1.06, 95% CI: 1.05 - 1.08) for both aortic valve stenosis and the need for valve replacement surgery (HR 1.06, 95% CI: 1.03 - 1.08). These findings highlight the significant and independent association between higher BMI influenced by genetic factors and heightened risks of aortic valve conditions necessitating medical intervention.
7	Tan et al, (2022)	The Cardiac Ageing Study, conducted from 2014 to 2017, involved 970 participants with an average age of 73 years. The study found that 124 individuals (12.8%) met the criteria for obesity based on BMI measurements, while 347 participants (35.7%) were classified as obese according to waist circumference measurements. Notably, the assessment based on waist circumference revealed a higher prevalence of obesity among women, particularly in the elderly age group. The study found that obesity, as determined by both BMI and waist circumference measurements, is significantly associated with myocardial relaxation disorders (E/A ratio) and

		cardiac fitness (Vo2 Max). Specifically, individuals classified as obese based on BMI criteria tend to have a notably lower E/A ratio compared to non-obese individuals (1.13 ± 0.46 vs 0.98 ± 0.35; $p < 0.001$). Additionally, individuals with a healthy BMI but elevated waist circumference exhibit greater left atrial volume (Left Aatrium) with a statistical significance of $p = 0.003$. These findings highlight the distinct impacts of BMI and waist circumference on cardiovascular parameters, underscoring their relevance in assessing cardiac health. Waist circumference is also a significant predictor of myocardial relaxation disorders, with a beta coefficient of -0.114 (standard error 0.024, $p < 0.001$). This underscores the substantial association between abdominal obesity and cardiovascular parameters, indicating that waist circumference is essential for assessing cardiac health beyond BMI alone.
8	Chien et al, (2021)	Obesity and malnutrition, characterized by high body mass index (BMI) and low skeletal muscle area (SA), are linked to more significant left ventricular remodeling and poorer diastolic function. This is reflected in higher left ventricular mass index (44.2 ± 1.52 vs 33.8 ± 8.28 gm/m²), lower tissue Doppler imaging early diastolic velocity (TDI-e0: 7.97 ± 2.16 vs 9.87 ± 2.47 cm/s), higher E/e' ratio (9.19 ± 3.01 vs 7.36 ± 2.31), and increased left atrial volume index (19.5 ± 7.66 vs 14.9 ± 5.49 mL/m²) compared to individuals with low BMI and high SA, as well as other subgroups ($p < 0.001$ for all comparisons). Moreover, they exhibited the highest risk, with a Hazard Ratio (HR) of 2.49 (95% CI 1.43 to 4.34, $p = 0.001$). These findings emphasize that both obesity and malnutrition, characterized by high BMI and low skeletal muscle area (SA), play significant roles in adverse cardiac remodeling and impaired diastolic function. They indicate a heightened cardiovascular risk associated with these body composition profiles compared to other studied groups.
9	Pandey et al, (2020)	The study analyzed the relationship between leisure-time physical activity (LTPA) and Body Mass Index (BMI) in 51,451 participants. Over the study period, there were 3,180 incidents of heart failure, categorized into HFpEF (1,252 cases), HFrEF (914 cases), and unclassified cases (1,014). The adjusted analysis showed a gradual association between BMI levels and the overall risk of heart failure, with higher BMI levels correlating with an elevated risk. Notably, the link between BMI and HFpEF risk was more pronounced and consistent

		compared to HFrEF risk. This suggests that BMI may have a more significant impact on predisposing individuals to HFpEF relative to HFrEF, indicating distinct effects of BMI on different types of heart failure The relationship between body mass index (BMI) and the risk of heart failure (HF) is complex and nuanced. Studies have shown that higher BMI levels are associated with a graded increase in the overall risk of HF. Overweight individuals exhibit a modest elevation in risk, with an adjusted hazard ratio (HR) of 1.18 (95% CI 1.08–1.30), while class I obesity shows a higher risk with an adjusted HR of 1.38 (95% CI 1.24–1.54). The greatest risk is observed among participants classified as obesity class II-III, with an adjusted HR of 2.19 (95% CI 1.94–2.48), compared to those with a normal BMI.However, when focusing on heart failure with reduced ejection fraction (HFrEF), the study reveals that only participants classified in obesity class II-III exhibit a significantly increased risk (adjusted HR 1.49, 95% CI 1.18–1.89). In contrast, overweight individuals and those in class I obesity do not show a significant difference in HFrEF risk compared to the normal-weight group. These findings underscore a nuanced association between BMI categories and heart failure risk, emphasizing that higher BMI categories are more predictive of overall heart failure risk rather than specifically HFrEF There exists a clear and graded relationship between BMI and the risk of heart failure with preserved ejection fraction (HFpEF), as observed across various BMI categories compared to individuals of normal weight. Adjusted hazard ratios (HR) demonstrated a 38% increased risk of HFpEF among those classified as overweight (BMI 25 to <30 kg/m²), with an HR of 1.38 (95% CI 1.18–1.61). Class 1 obesity (BMI 30 to <35 kg/m²) showed a 56% higher risk, with an HR of 1.56 (95% CI 1.30–1.87). The risk escalated significantly in obesity class II-III (BMI ≥35 kg/m²), where the HR was markedly elevated at 2.72 (95% CI 2.24–3.32). Participants categorized as extremely obese (BMI ≥35 kg/m²) demonstrated the highest risk not only for HFpEF but also for heart failure with reduced ejection fraction (HFrEF). These findings emphasize a distinct association between higher BMI categories and increased risk of HFpEF, with obesity class II-III identified as the highest-risk group across both HFpEF and HFrEF.
10	Caleyachetty et al, (2017)	Data extracted from The Health Improvement Network (THIN) database, spanning from 1995 to 2015, encompassed 3.5 million adults aged 18 years and above without prior

		cardiovascular disease history. The study categorized participants into BMI groups: underweight, normal weight, overweight, and obese categories. Its objective was to assess the relationship between BMI and the risk of three metabolic disorders: diabetes, hypertension, and hyperlipidemia. During a median follow-up period of 5.4 years, individuals classified as obese but without any of the studied metabolic disorders showed notably higher risks compared to normal-weight individuals who did have these disorders. Specifically, in comparison to normal-weight individuals with metabolic disorders, obese individuals without these conditions had a 49% increased risk of coronary heart disease (HR: 1.49, 95% CI: 1.45–1.54), a 7% higher risk of cerebrovascular disease (HR: 1.07, 95% CI: 1.04–1.11), and nearly double the risk of heart failure (HR: 1.96, 95% CI: 1.86–2.06). Furthermore, the likelihood of developing coronary heart disease, cerebrovascular disease, and heart failure progressively rose across normal-weight, overweight, and obese categories as the number of metabolic disorders increased. These findings underscore the significant impact of both BMI and metabolic health on cardiovascular risks, highlighting the intricate interplay between body size phenotypes and metabolic disorders in determining outcomes related to cardiovascular disease.
11	Mongraw-Chaffin et al, (2022)	A study involving 6,809 participants indicated that early-stage metabolically healthy obesity (MHO) did not show a significant association with increased cardiovascular disease (CVD) incidence compared to metabolically healthy individuals of normal weight. However, nearly half of the participants developed metabolic syndrome (MetS) during the follow-up period, suggesting that MHO often transitions over time. Individuals with unstable MHO had a 60% higher likelihood of developing CVD (odds ratio [OR]: 1.60; 95% confidence interval [CI]: 1.14 to 2.25) compared to those with stable MHO or consistently healthy normal weight. The study found a clear and increasing relationship between the duration of metabolic syndrome (MetS) and the risk of cardiovascular disease (CVD), demonstrating a significant linear trend. Participants diagnosed with MetS once had an odds ratio (OR) of 1.62 (95% CI: 1.27 to 2.07), those diagnosed twice had an OR of 1.92 (95% CI: 1.48 to 2.49), and those diagnosed three or more times had the highest OR of 2.33 (95% CI: 1.89 to 2.87). These associations were highly

		statistically significant, with p-values for trends all below 0.001. Furthermore, the study highlighted that metabolic syndrome (MetS) accounted for approximately 62% (ranging from 44% to 100%) of the association between obesity at any point during the follow-up period and the development of cardiovascular disease (CVD). This underscores the critical role of metabolic health, particularly the stability of MetS over time, in influencing cardiovascular risk among individuals classified as metabolically healthy obese (MHO).
12	Pfaller et al, (2021)	In a study involving 790 pregnancies, the distribution of body mass index (BMI) among women was as follows: 19% were classified as obese (BMI ≥ 30 kg/m²), 25% were overweight (BMI 25 to 29.9 kg/m²), 53% were normal-weight (BMI 18.5-24.9 kg/m²), and 3% were classified as thin (BMI < 18.5 kg/m²). Obese women experienced significantly higher rates of pregnancy complications, specifically cesarean delivery (CE), compared to normal-weight women (23% vs. 14%; p = 0.006). In the multivariate analysis, both obesity (odds ratio: 1.7; 95% confidence interval: 1.0 to 2.7) and elevated CARPREG II scores (Canadian Cardiac Disease in Pregnancy Study II) (odds ratio: 1.7; 95% confidence interval: 1.5 to 1.9) independently correlated with increased odds of cesarean delivery. Furthermore, obese women exhibited a higher incidence of pre-eclampsia compared to those with normal weight (8% vs. 2%; p = 0.001). These findings underscore the significant risks associated with obesity during pregnancy, including elevated rates of cesarean delivery and a greater prevalence of pre-eclampsia. This highlights the importance of addressing weight management and health conditions both before and during pregnancy to optimize maternal and fetal health outcomes.

Discussion

Factors Influencing the Prognosis of Heart Disease in Obesity

The Framingham Study has established obesity as a significant risk factor for heart disease through extensive epidemiological research. However, conflicting findings exist in various studies regarding whether obesity directly causes heart disease independently. This systematic review consolidates multiple scientific articles that investigate obesity and its interactions with other factors influencing heart disease risk. The review identifies several critical elements that impact the relationship between obesity and heart disease, such as genetic predispositions, levels of physical activity, presence of metabolic disorders like diabetes, history of prior heart disease, nutritional status, distribution of body fat, and fluctuations in body mass index. Together, these

factors collectively contribute to determining the overall risk of developing heart disease.

The systematic review highlights the multifaceted impact of obesity on cardiovascular health, encompassing various heart-related issues and clinical outcomes. The comprehensive analysis synthesizes evidence from diverse studies to illustrate the intricate interplay of factors contributing to the development and progression of heart disease. Key aspects covered include:

1. **Cardiac Remodeling**: Obesity leads to structural and functional changes in the heart, including left ventricular hypertrophy (LVH) and dilation, which can result in diastolic and systolic dysfunction.
2. **Aortic Stenosis (AS)**: Obesity is associated with an increased risk of aortic stenosis, which can further exacerbate cardiovascular complications.
3. **Coronary Artery Calcification (CAC)**: Excessive adipose tissue accumulation is linked to increased coronary artery calcification, a significant risk factor for coronary heart disease.
4. **Heart Function**: Obesity affects cardiac function by altering blood volume, plasma volume, and cardiac output, leading to increased wall tension and potentially systolic dysfunction.
5. **Clinical Events**: Obesity is a major risk factor for various cardiovascular events, including heart failure (HF), coronary heart disease, cerebrovascular disease, hospitalization, and mortality.
6. **Mortality**: Obesity is associated with increased morbidity and mortality rates, with a significant impact on overall survival.

The review underscores the complex interplay of factors that contribute to the development and progression of heart disease in obese individuals, emphasizing the need for comprehensive understanding and effective interventions to mitigate these risks.

Body Mass Index (BMI) as a Biomarker of Obesity to Predict CVD

The World Health Organization (WHO) defines obesity based on body mass index (BMI), classifying individuals with a BMI above 30 kg/m² as obese. A comprehensive study involving approximately 3.5 million participants in the UK categorized them by BMI (underweight, normal-weight, overweight, and obesity) and metabolic health status (presence of diabetes, hypertension, and hyperlipidemia). Over a study period of 5.4 years, the research assessed the risk of cardiovascular diseases (CVD), including coronary artery disease (CAD), cerebrovascular disease, heart failure (HF), and peripheral vascular disease (PVD) among all participants. The study found that individuals with obesity were at a higher risk of developing these cardiovascular diseases compared to those with normal weight or overweight. This underscores the importance of maintaining a healthy BMI and metabolic health to reduce the risk of cardiovascular complications.

The study results indicated that obese individuals without metabolic disorders faced significantly higher risks compared to non-obese individuals without these health issues. Specifically, they had a 49% increased risk of coronary artery disease (CAD) (adjusted hazard ratio [aHR]: 1.49; 95% confidence interval [CI]: 1.45 – 1.54), a 7% higher risk of cerebrovascular disease (aHR: 1.07; 95% CI: 1.04 – 1.11), and nearly double the

risk of heart failure (HF) (aHR: 1.96; 95% CI: 1.86 – 2.06). These findings underscore the independent impact of obesity, defined by BMI, on the incidence of major cardiovascular diseases, even in the absence of metabolic health issues. They emphasize the critical need to address obesity as a significant public health concern to mitigate the burden of cardiovascular disease (CVD) (Caleyachetty et al., 2017).

Two meta-analyses involving large participant cohorts, totaling 250,016 and 414,587 individuals, respectively, suggested an 'obesity paradox' in people with type 2 diabetes mellitus (T2DM), where being overweight or obese seemed to offer protection against cardiovascular disease (CVD). This paradox could be attributed to limitations in these studies' ability to track different patterns of obesity progression over time accurately. Polemiti et al. (2021) conducted a study involving 1,083 participants in Europe to investigate how body weight and changes in weight relate to the development of microvascular and macrovascular complications in individuals with T2DM. Their findings indicated that baseline BMI did not significantly affect the risk of microvascular or macrovascular complications among those with T2DM. However, a reduction in BMI of at least 1% was linked to a decreased risk of total microvascular complications (HR 0.62; 95% CI 0.47–0.80), nephropathy (HR 0.57; 95% CI 0.40–0.81), and neuropathy (HR 0.73; 95% CI 0.52–1.03) compared to individuals whose BMI remained stable.

These results imply that although the obesity paradox might be observed in specific scenarios like cardiovascular disease risk in type 2 diabetes, actively managing weight and achieving BMI reductions could lower the risk of microvascular complications associated with diabetes.

Other Obesity Biomarkers to Predict CVD

Obesity poses a substantial risk for cardiometabolic diseases such as type 2 diabetes mellitus (T2DM), cardiovascular disease (CVD), and various cancers, which are increasingly recognized as significant global health challenges. While body mass index (BMI) is commonly used to classify obesity, its effectiveness in predicting cardiovascular disease risk has been questioned. BMI lacks consideration for fat distribution and cannot differentiate between weight gained from fat versus muscle mass. Consequently, researchers are currently engaged in epidemiological investigations aimed at identifying obesity biomarkers that offer more precise predictions of clinical outcomes across a spectrum of cardiovascular diseases compared to BMI assessments.

Coronary artery disease (CAD) ranks among the primary causes of sudden death worldwide, and the assessment of coronary artery calcification scores (CACS) through CT scans is widely recognized for its reliability in detecting CAD (Ahmad & Anderson, 2021). A retrospective cohort study by Lee et al. (2021) In a study conducted in South Korea with 1,015 healthy participants, it was found that individuals with a BMI of 25 kg/m² or higher, greater waist circumference (WC), and a high ratio of visceral adipose tissue (VAT) to subcutaneous adipose tissue (SAT) were predictive factors for the progression of coronary artery calcification (CAC). Among these factors, a VAT/SAT ratio of 30% or more emerged as the most robust predictor, showing a significant association with CAC progression (adjusted hazard ratio of 2.20; $p < 0.001$).

Additionally, Tan et al. (2022) conducted a prospective cohort study involving 970 participants with an average age of 73 ± 4 years, which revealed a link between obesity and alterations in cardiovascular structure and function. The research found that

increased waist circumference (WC) independently correlated with diminished cardiac function, as measured by VO2 max, and impaired heart muscle relaxation, assessed using echocardiography to determine the E/A ratio for diastolic left ventricular function. In contrast, body mass index (BMI) did not demonstrate any association with compromised heart function or structural cardiac changes.

Oh et al. (2020) Data from 9,460 participants enrolled in the Korean Genome and Epidemiology Study, a prospective cohort investigation in South Korea, were examined. Obesity classifications were based on the Asia-Pacific BMI criteria (BMI ≥ 25 kg/m²), while body shape was evaluated using the z-score of the log-transformed body shape index (LBSIZ). Metabolic health status was determined according to the Adult Treatment Panel-III (ATP-III) criteria. Participants were categorized into four distinct groups: metabolically healthy non-obese (MHNO), metabolically healthy obese (MHO), metabolically unhealthy non-obese (MUNO), and metabolically unhealthy obese (MUO).

The findings indicated that participants classified in the MUO group demonstrated the highest likelihood of developing cardiovascular disease (CVD). Notably, individuals in the MHO and MHNO groups showed comparable risks for CVD (HR: 1.29; 95% CI: 0.96–1.73). Importantly, using LBSIZ as a measure of body shape effectively differentiated the risk of CVD, providing additional insights beyond traditional BMI classifications and metabolic health status.

The Asian Sudden Cardiac Death in Heart Failure (ASIAN-HF) registry encompassed 5,964 patients across 11 Asian countries, including Taiwan, Hong Kong, China, India, Malaysia, Thailand, Singapore, Indonesia, Philippines, Japan, and South Korea. This registry was conducted at 46 research centers and enrolled patients between October 1, 2016, and October 6, 2016. The registry aimed to investigate heart failure categorized into three types based on systolic function: HFrEF (HF with reduced ejection fraction, < 40%), HFmrEF (HF with mid-range ejection fraction, 40-49%), and HFpEF (HF with preserved ejection fraction, ≥ 50%).

The ASIAN-HF study categorized patients into four groups based on their body mass index (BMI) and waist-to-height ratio (WHtR): Obese-Thin (BMI ≥ 24.5 kg/m² and WHtR < 0.55), Overall Obese (BMI ≥ 24.5 kg/m² and WHtR ≥ 0.55), Overall Lean (BMI < 24.5 kg/m² and WHtR < 0.55), and Lean-Fat (BMI < 24.5 kg/m² and WHtR ≥ 0.55). Patients in the Lean-Fat group were predominantly female (35.4%) and more likely to reside in low-income countries (47.7%). They also exhibited a higher prevalence of diabetes (46%) and reported a lower mean quality of life score (63.3 ± 24.2). Furthermore, they experienced elevated rates of mortality and hospitalization due to heart failure (22%).

Multivariate regression analysis revealed that individuals in the Lean-Fat group faced the highest risk compared to the other categories (adjusted hazard ratio [aHR] 1.93, 95% CI 1.17–3.18, p = 0.01). This heightened risk was consistent across both HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF), indicating that the Lean-Fat phenotype significantly influences heart failure outcomes. The findings suggest that the Lean-Fat group, characterized by low BMI and high WHtR, is associated with the worst outcomes in patients with heart failure, underscoring the importance of considering both BMI and WHtR in assessing cardiovascular risk.

Other Factors that Can Predict CVD in Obesity Conditions

Genetic factors play a crucial role in determining susceptibility to obesity, influenced by specific single nucleotide polymorphisms (SNPs) that impact weight gain. Identified SNPs include FTO (rs9939609), MC4R (rs17782313), TMEM18 (rs6548238), BDNF (rs10767664), and GNPDA2 (rs10938397). These SNPs collectively contribute to an unweighted allele score that categorizes individuals based on the number of risk alleles they carry: 0–3 alleles (9% of the population), four alleles (19%), 5–6 alleles (52%), and 7–10 alleles (20%).

Research has shown that individuals with a higher genetic predisposition to obesity, as measured by the number of alleles, tend to have a significantly higher body mass index (BMI). Specifically, those in the 7–10 alleles group have a BMI that is 0.87 kg/m² higher compared to those in the 0–3 alleles group. Furthermore, each 1 kg/m² increase in BMI is associated with a higher risk of aortic valve stenosis and replacement. The relative risks (RR) for these conditions are 1.52 (95% CI: 1.23–1.87) and 1.49 (95% CI: 1.07–2.08), respectively. Additionally, each 1 kg/m² rise in BMI is correlated with a higher hazard ratio (HR) for these conditions, with values of 1.06 (95% CI: 1.05–1.08) and 1.06 (95% CI: 1.03–1.08). These findings underscore the substantial influence of genetic predisposition on health outcomes related to obesity, such as cardiovascular disease.

Besides genetic factors, several variables influence the risk of cardiovascular disease (CVD) and related heart disorders, including malnutrition, physical activity levels, and metabolic diseases. Obese individuals with malnutrition (defined as BMI ≥ 25 kg/m² and serum albumin [SA] < 45 g/L) tend to show more severe cardiac remodeling. This is indicated by a higher left ventricular mass index (44.2 ± 1.52 vs. 33.8 ± 8.28 gm/m²) and relative wall thickness (0.39 ± 0.05 vs. 0.38 ± 0.06). They also typically exhibit poorer diastolic function, characterized by lower tissue Doppler imaging velocity (TDI-e0: 7.97 ± 2.16 vs. 9.87 ± 2.47 cm/s), a higher E/e0 ratio (9.19 ± 3.01 vs. 7.36 ± 2.31), and increased left atrial volume index (19.5 ± 7.66 vs. 14.9 ± 5.49 mL/m²), compared to individuals with a normal BMI and higher SA levels. These findings underscore the intricate interplay between obesity, nutritional status, and cardiovascular health, underscoring the detrimental impact of malnutrition in obese populations on both heart structure and function.

In a study by Pandey et al. (2020), it was found that a decrease in leisure-time physical activity (LTPA) independently correlates with higher BMI and an increased risk of heart failure (HF) in a cohort comprising 51,451 individuals. Their multivariate regression analysis consistently showed that increasing LTPA and decreasing BMI were associated with a reduced risk of heart failure with preserved ejection fraction (HFpEF) compared to heart failure with reduced ejection fraction (HFrEF).

In a study conducted by Mongraw-Chaffin et al. (2022), involving 6,809 participants observed over a median follow-up of 12.2 years, researchers investigated whether individuals initially categorized as metabolically healthy obese (MHO) transitioned to metabolic syndrome (MetS) and how the duration of MetS impacted mortality risk. This study aimed to explore the relationship between MHO as a potential transitional state towards MetS and its implications for cardiovascular disease (CVD) risk.

Individuals classified as metabolically healthy obese (MHO) did not exhibit a statistically significant association with cardiovascular disease (CVD) incidence compared to metabolically healthy normal-weight individuals (MHN). However, nearly half of those initially categorized as MHO experienced transitions to metabolic syndrome (MetS) during the follow-up period, indicating an unstable MHO status. Those with unstable MHO status showed a significantly increased risk of developing CVD (odds ratio [OR]: 1.60, 95% CI 1.14–2.25) compared to individuals who maintained stable MHO status. Additionally, there was a clear dose-response relationship observed between the duration of MetS and the risk of CVD: individuals with MetS detected during 1, 2, and 3 or more visits had odds ratios (ORs) of 1.62 (95% CI 1.27–2.07), 1.92 (95% CI 1.48–2.49), and 2.33 (95% CI 1.89–2.87), respectively, indicating a progressively higher risk with longer duration of MetS. This underscores the importance of considering the stability of MHO status and the duration of MetS in assessing the risk of CVD (Mongraw-Chaffin et al., 2022).

CONCLUSION

This research emphasizes that while obesity is linked to cardiovascular disease (CVD) risk, this relationship is influenced by various factors beyond BMI alone. Genetic predisposition, physical activity levels, metabolic disorders, prior heart disease history, nutritional status, fat distribution, and changes in BMI all play significant roles in determining the prognosis of heart disease. BMI alone is insufficient to reliably predict CVD risk due to its inability to differentiate between muscle mass and fat accumulation. Studies underscore that metrics such as fat distribution indicators (waist circumference, waist-to-height ratio, log-transformed body shape index [LBSIZ], ratio of visceral adipose tissue [VAT] to subcutaneous adipose tissue [SAT]) provide better predictive value for CVD risk in individuals with obesity compared to BMI alone. Moreover, there remains a need for further research to explore the specific cardiovascular risks associated with obesity, particularly given the frequent co-occurrence of metabolic disorders in obese individuals.

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