Association Between Insulin Resistance with Body Mass Index and Glycated Haemoglobin: Meta Analysis and Systematic Review

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Abstract
Obesity, indicated by Body Mass Index is a risk factor for type 2 diabetes through the stimulation of insulin resistance. However, its association with glycated haemoglobin is a crucial indicator of blood-sugar control, and may vary across different populations and disease statuses. This systematic review and meta-analysis were performed to study the association between insulin resistance with body mass index and glycated haemoglobin values. This study was carried out in a database of PubMed search by using main keywords including insulin, insulin resistance, risk factor, obesity. Articles were collected from randomized controlled trials for reports based on inclusion criteria like study design and measure of insulin resistance, body mass index, glycated haemoglobin and that were published between 2012 and 2022. The meta-analysis was performed through Revman 5.4.1 software using a fixed effect model. continuous data are expressed as the mean difference with 95% confidence interval to summarize the effect size across studies. Among 351 studies reviewed, only 9 studies met the inclusion criteria and quantitative data from 580 participants were analysed, 320 in the intervention group and 260 in the control group. The mean difference for Body Mass Index was -0.71 [95% CI -0.89, -0.52] and glycated haemoglobin was -0.48 [95%CI -0.65, -0.31]. This systematic review's results with meta-analysis showed evidence for a significant association between insulin resistance with Body Mass Index and Glycated Haemoglobin values. In conclusion, this systematic review and meta-analysis investigated the relationship between IR with BMI and HbA1c values across various studies and found a positive association.

Keywords:
Insulin Resistance; Body Mass Index; Glycated Hemoglobin; Obesity; Type 2 Diabetes Mellitus; Homeostatic Model Assessment of Insulin Resistance.

Introduction

Insulin resistance (IR) arises when the nutrient storage pathways, evolved to maximize efficient energy utilization, are exposed to chronic energy surplus. The pathophysiology of insulin resistance: (i) Tissue involvement – all tissues with insulin receptors can become insulin resistant, but the primary drivers are the liver, skeletal muscle, and adipose tissue and; these tissues play a crucial role in glucose metabolism and insulin sensitivity. (ii) Impaired insulin signalling – ectopic lipid accumulation in the liver and skeletal muscle triggers pathways that impair insulin signalling and; this leads to reduced muscle glucose uptake and decreased hepatic glycogen synthesis. (iii) Hyperinsulinemia – IR results in a compensatory increase in beta-cell insulin production and; this leads to hyperinsulinemia, where there is an excess of insulin in circulation. (iv) Metabolic consequences – hyperglycemia (due to impaired glucose disposal), hypertension (IR affects blood pressure regulation), dyslipidemia (altered lipid metabolism), hyperuricemia (elevated uric acid levels), Inflammation (elevated inflammatory markers), endothelial dysfunction (impaired blood vessel function) and prothrombotic state (increased risk of blood clot formation). Type 2 Diabetes Mellitus (T2DM) – The predominant consequence of insulin resistance is T2DM. IR often precedes T2DM by 10 to 15 years. Management includes lifestyle modifications (focus on nutrition like calorie reduction, avoiding excessive carbohydrate intake) as well as physical activity and medications (some drugs improve insulin response and reduce insulin demand). Finally, complications like vascular complications and non-alcoholic fatty liver disease are common [1, 2, 3].

IR may be difficult to detect during its initial phases, but as it persists and blood sugar levels remain elevated, symptoms may gradually emerge. Some common signs associated with IR are: (i) polydipsia; (ii) polyuria; (iii) blurry vision and (iv) unusual tiredness. IR can lead to various complications like (i) coronary artery disease; (ii) polycystic ovary syndrome; (iii) metabolic syndrome; (iv) prediabetes and (v) T2DM; and (vi) fatty liver disease [4]. IR can be managed through a combination of either lifestyle changes like weight management, regular exercise, diet and adequate sleep and/ or medications like metformin and pioglitazone, and/ or bariatric surgery and/ or self-care practices like monitoring of blood sugar levels regularly and maintaining a balanced diet rich in fruits, vegetables as well as whole grains and stay physically active [5, 6, 7)]. IR impairs the ability of body's cells to utilize and deposit glucose and triglycerides, that resulting in excessive levels circulating in the bloodstream [8] and leading to chronic hyperinsulinemia, hyperglycemia-induced β-cell failure, and eventually to T2DM [9]. Type 2 diabetes, cardiovascular disease, essential hypertension, polycystic ovarian syndrome, non-alcoholic fatty liver disease, some types of cancer, and sleep apnoea are among the clinical syndromes linked to insulin resistance [10].

BMI indicating overweight (BMI ≥ 25 kg/ m2)is considered the leading risk factor for T2DM [11]. In 2021, high BMI contributes more than 50% of the global T2D disability-adjusted life year. In 2021, there were 529 million people of all ages worldwide living with diabetes, and the global age-standardized prevalence is 6.1%, which increased by 90.5% from 3.2% in1990, and is expected to reach 9.8%, affecting 13.1 billion people. It is noteworthy that T2D accounts for more than 96% of all [12]. HbA1c in blood provides evidence about an individual's average blood glucose levels during the previous two to three months, which is the predicted half-life of red blood cells ([13].

The HbA1c is now recommended as a standard of care for testing and monitoring diabetes, specifically T2DM [14].

In 1958, HbA1c was first isolated by Huisman et al., and later 1976, Koenig et al., was first proposed using the HbA1c as a biomarker for monitoring the levels of glucose among diabetic patients [15, 16]. Prediabetes usually has the HbA1c levels between 5.7% and 6.4%, while those with < 6.4% HbA1c levels have diabetes [17, 18]. Since diabetes is associated with several comorbidities, the recommendations for individuals with diabetes include a healthy lifestyle (diet and exercise) and maintaining the HbA1c levels below 7.0%. Diabetes-related complications are directly proportional to the levels of HbA1c – the increase in the HbA1c levels also increases the risk of such complications [19].

Epidemiological studies such as the US Physicians Health Study have reported substantial decreases in the relative risk of type 2 diabetes with lifelong regular physical activity [20]. Large scale randomised controlled clinical trials such as the Diabetes Prevention Program [21] and the Finnish Prevention Study demonstrate a 58% reduction in progression of impaired glucose tolerance to type 2 diabetes by intensive lifestyle modification which included a minimum of 20–30 minutes of exercise per day [22]. The aim of the present systematic review and meta-analysis study is to investigate the association between insulin resistance with body mass index and glycated haemoglobin values. The aim of the present systematic review and meta-analysis study is to investigate the association between insulin resistance and body mass index.

2. Methodology

2.1. Study Design and Search Strategy

The present systematic review and meta-analysis guidelines outlined in the preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement by integrating the results from relevant studies [23]. The study aimed to determine whether insulin resistance is associated with body mass index and glycated haemoglobin. The authors conducted comprehensive literature research on the insulin resistance and body mass index and glycated haemoglobin through PubMed database over the previous ten years (between January 2012 and December 2022). The search strategy included the following keywords like insulin resistance, insulin, risk factor and obesity. This study uses the following filters like free full text, randomized controlled trial, humans, English, both genders, adults and above 19+ years of age [24].

2.2. Study Selection

All studies were selected based on their title, abstract and free full texts of the materials. All eligible abstracts were considered only when full manuscript data extraction if the study met all the following criteria: (i) reported with BMI and HbA1C values (mean ±SD); (ii) adults from both genders; (iii) age ≥19 years; (iv) randomized controlled trial study design. Few studies were excluded: (i) literature review (n=1); (ii) abstract (n=1); (iii) duplicate abstracts and (iv) without HOMA-IR (n=11). Finally, 9 studies were selected to carry out the meta-analysis.

2.3. Data Extraction

The following data were extracted from the selected studies: (i) first author & year of publication; (ii) setting and population; (iii) study design and sample size; (iv) age and (v) BMI (Kg/m^2); (vi)

HbA1c (%). A statistical measure used in meta-analysis, particularly I^2 is used to assess heterogeneity across the studies. Meta-regression analysis was not conducted due to a small sample size, with fewer than 10 studies per covariate [25]. Publication bias was analyzed using funnel plots, based on the standard mean difference to visually assess asymmetry and detect potential bias in the included studies. To evaluate the robustness of our results, we performed a sensitivity analysis by sequentially excluding each study from the pool of studies to assess its effect on the overall findings.

2.4. Statistical Analysis

The data were analyzed using Revman 5.4.1 software, with continuous outcome variables presented as mean differences and 95% confidence intervals, applying a fixed-effects model depending on the level of heterogeneity across studies. The p-value was used to indicate statistical significance, where a p-value typically <0.01, indicated a significant difference between the groups if the diamond shape did not overlap the line of no effect. The inconsistency index (I^2) was used to assess statistical heterogeneity among the included studies.

Table 1: Characteristics of the included studies for BMI and HbA1c

Author Name, Year	Setting	Study Design	Total	Mean Age (Years)	BMI (kg/m^2)		HbA1c (%)	
					Exp Mean (SD)	Con Mean (SD)	Exp Mean (SD)	Con Mean (SD)
Brennan AM et al., 2020 [26]	Single	RCT	61	68.6	38.94 (3.41)	36.37 (4.97)	6.39 (1.84)	6.17 (0.7)
Basu A et al., 2021 [27]	Multiple	RCT	33	53	32.0 (2.4)	32.0 (2.4)	5.5 (0.2)	5.5 (0.3)
Hajj CE et al., 2020 [28]	Single	RCT	88	66.3	21.2 (1.1)	24.1 (4.89)	6.53 (0.63)	6.64 (1.31)
Jahansouz C et al., 2018 [29]	Multiple	RCT	63	50.5	29 (1.35)	35.9 (2.95)	6.7 (0.4)	9.5 (1.05)
Abbate M et al., 2021 [30]	Single	RCT	128	50	31.5 (3.6)	33.6 (3.6)	5.8 (0.9)	6.0 (1.2)
Umphonsathien M et al., 2022 [31]	Single	RCT	40	45	27.6 (1.5)	27.1 (1.6)	6.6 (0.25)	6.9 (0.3)
Njembe MTN et al., 2021 [32]	Single	RCT	24	55	25.8 (1.16)	26.01 (0.79)	6.34 (0.18)	6.3 (0.13)
Kruschitz R et al., 2020 [33]	Single	RCT	50	NR	28.2 (3.8)	43.8 (4.3)	5.4 (0.7)	6 (1.3)
Zhang X et al., 2022 [34]	Single	RCT	93	45	32.2 (0.62)	32.9 (0.62)	5.54 (0.06)	5.60 (0.067)

NR – Reported; EXP: Experiment; CON: Control; SD: Standard Deviation;
BMI: Body Mass Index; HbA1c: Glycated Haemoglobin

Fig. 1: Risk of bias graph of review authors' judgements about each risk of bias item presented as percentages across all included studies selected for the IR vs BMI

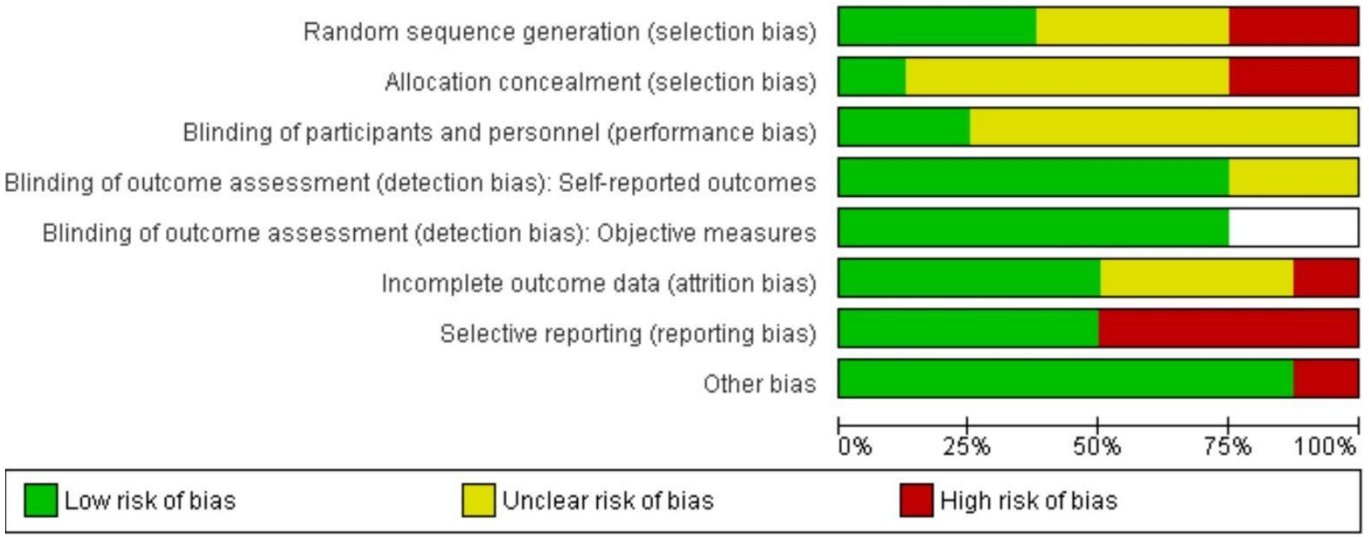
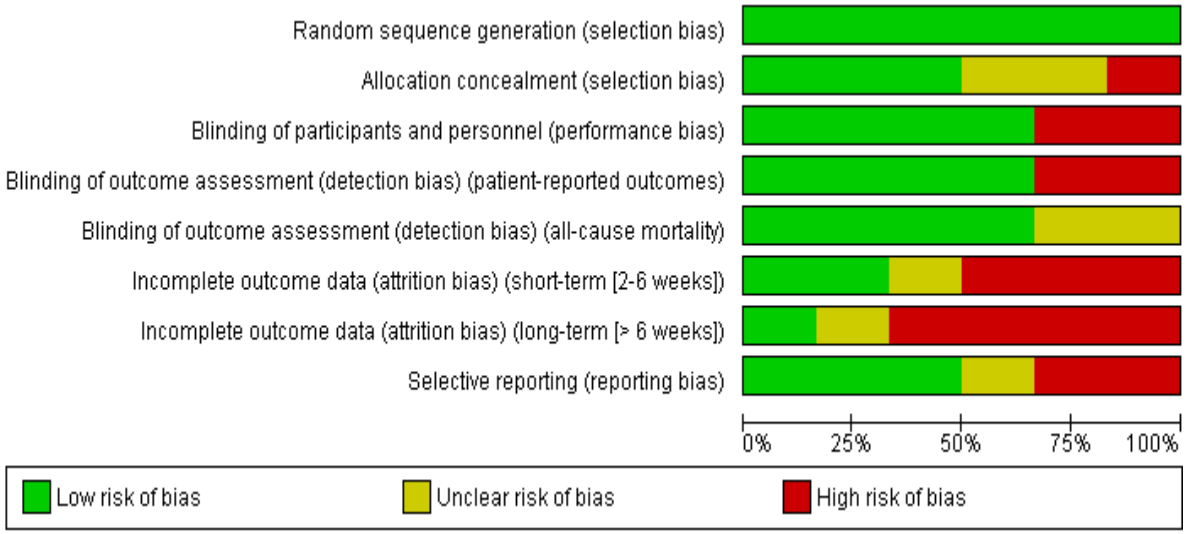


Fig. 2: Risk of bias graph of review authors' judgements about each risk of bias item presented as percentages across all included studies selected for the IR vs HbA1c


Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias) (patient-reported outcomes)
Blinding of outcome assessment (detection bias) (all-cause mortality)
Incomplete outcome data (attrition bias) (short-term [2-6 weeks])
Incomplete outcome data (attrition bias) (long-term [> 6 weeks])
Selective reporting (reporting bias)
0%
25%
50%
75%
100%
Low risk of bias
Unclear risk of bias
High risk of bias

Results

The risk-of-bias summary chart for the association between IR vs BMI (Fig. No. 1), assesses various types of biases in studies using a color-coded system, where green indicates a low risk, yellow represents an unclear risk, and red signifies a high risk. Overall, many studies exhibit a low risk of bias in areas such as blinding of outcome assessment (objective measures), incomplete outcome data, and other biases. However, concerns arise in specific domains like allocation concealment and selective reporting, where a significant proportion of studies show either unclear or high risk. Performance bias, related to the blinding of participants and personnel, is particularly marked by an unclear risk, suggesting possible gaps in study methodology or reporting. Similarly, self-reported outcomes show variability, with a mix of low and unclear risk. The presence of high-risk ratings, especially in selective reporting and allocation concealment, highlights potential methodological weaknesses that could influence the reliability of the studies. Addressing these biases through improved study design and transparent reporting is essential for ensuring more robust and trustworthy research findings.

The risk-of-bias summary chart for the association between IR vs HbA1c (Fig. No. 2) evaluates different types of biases in studies using a color-coded system, where green represents a low risk, yellow indicates an unclear risk, and red signifies a high risk. The chart shows that random sequence generation and allocation concealment, which relate to selection bias, have mostly low risk, though allocation concealment has some unclear and high-risk elements. Performance bias, linked to blinding of participants and personnel, exhibits a mix of low and unclear risk. Detection bias, assessed through blinding of outcome assessment for patient-reported outcomes and all-cause mortality, is mostly low risk, though patient-reported outcomes show some unclear risks. Attrition bias is divided into short-term (2–6 weeks) and long-term (>6 weeks), with short-term attrition bias having a mix of low, unclear, and high risk, while long-term attrition bias shows a higher proportion of high risk. Selective reporting (reporting bias) is a significant concern, with a notable portion of studies marked as high risk. Overall, while many studies maintain a low risk of bias, concerns remain in areas like selective reporting, long-term attrition bias, and allocation concealment, which could affect the reliability and validity of the findings.

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram (Fig. No. 3) outlines the systematic process of study selection for a meta-analysis. The process began with 351 records identified through database searching. After removing 18 duplicate records, 333 remained for screening. Following the initial screening, 283 records were excluded, leaving 50 full-text articles for detailed eligibility assessment. Upon full-text review, 41 articles were excluded based on predefined criteria, resulting in 9 studies being included in the qualitative synthesis. These same 9 studies were also incorporated into the quantitative synthesis (meta-analysis). The PRISMA diagram effectively demonstrates how the initial large pool of potential studies was systematically narrowed down to a final set of studies that met all inclusion criteria, ensuring transparency and rigor in the systematic review process.

Fig. No. 3: PRISMA flowchart of the study selection for the parameters

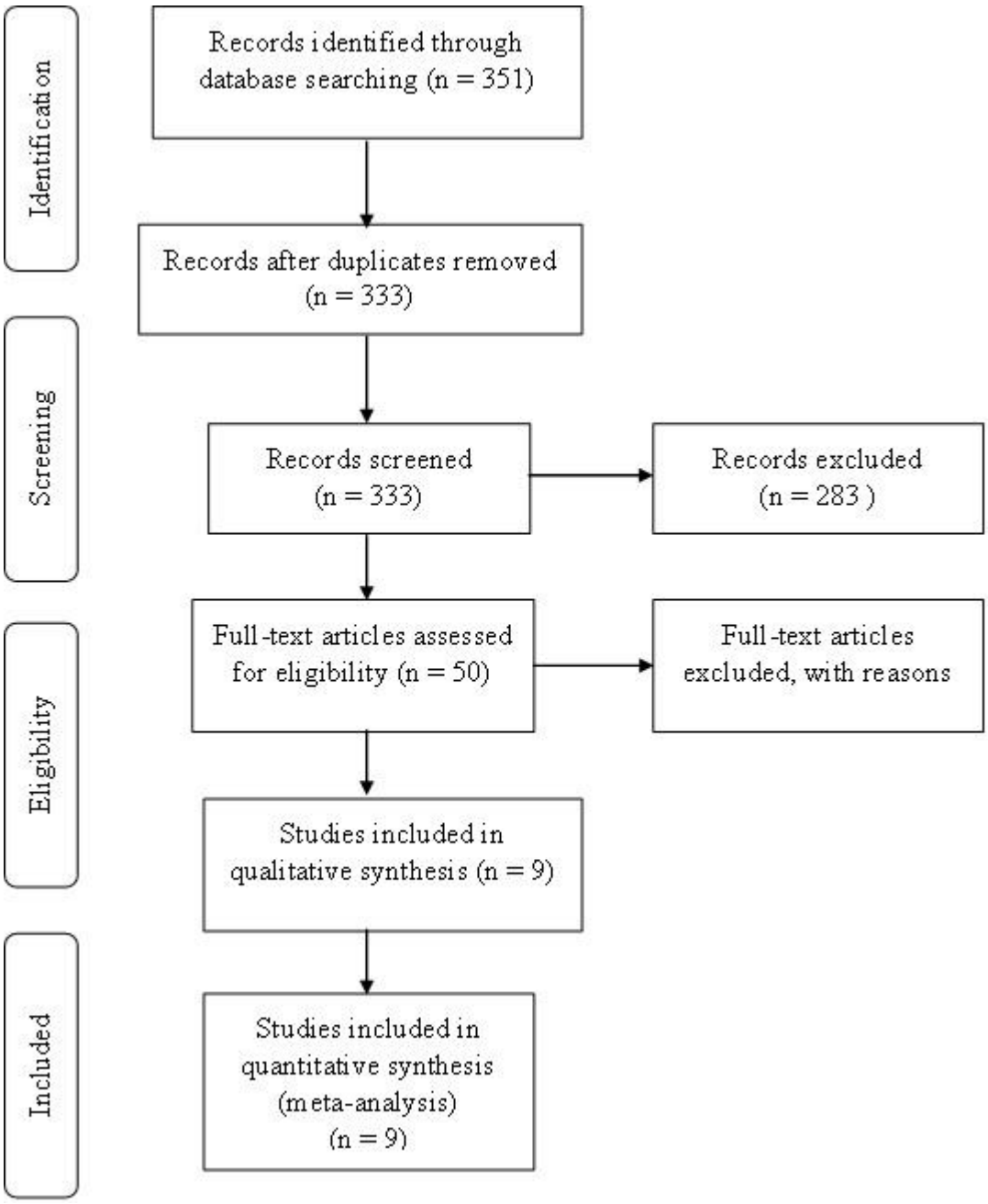
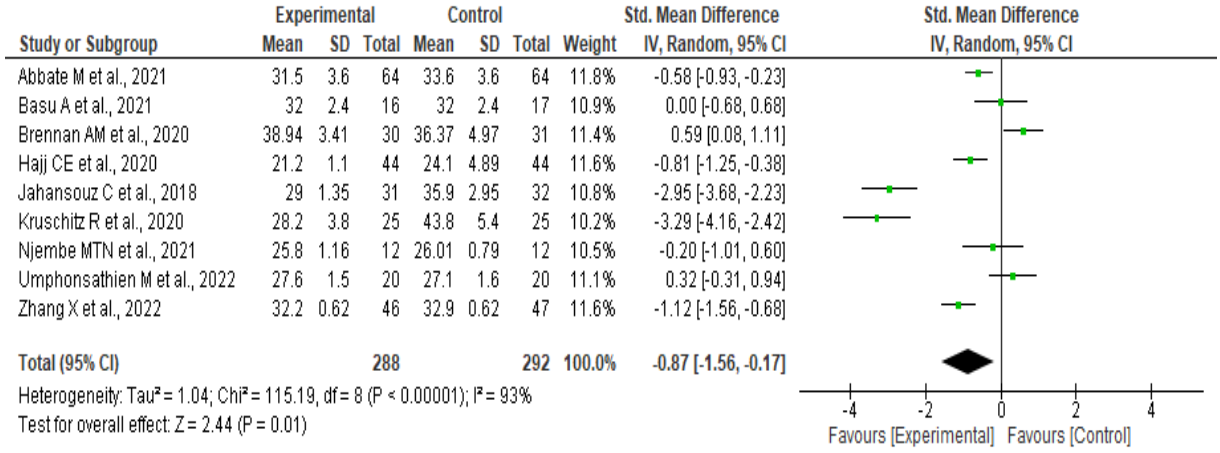


Fig. No. 4: Forest Plot to compare of the risk of IR and BMI between the two groups



The forest plot (Fig. No. 4) represents a meta-analysis comparing experimental and control groups across multiple studies between IR versus BMI. The left section lists the included studies along with their mean, standard deviation (SD), and sample size for both groups. Each study's contribution to the overall effect is indicated by its weight percentage. The middle section presents the standardized mean difference (SMD) using the inverse variance method under a random-effects model, along with its 95% confidence interval (CI). The right section graphically displays the effect sizes, where green squares represent individual study estimates, horizontal lines depict their 95% CI, and the diamond at the bottom summarizes the overall effect size. The meta-analysis reports an overall SMD of -0.87 [95% CI: -1.56 to -0.17], suggesting a statistically significant effect favouring the experimental group since the confidence interval does not include zero. However, high heterogeneity is observed (I^2 = 93%, Chi^2 = 115.19, $P < 0.00001$), indicating substantial variability among studies. The test of the overall effect ($Z = 2.44$, $P = 0.01$) confirms statistical significance, though the high heterogeneity suggests that study differences should be further explored.

The funnel plot (Fig. No. 5) is used to assess publication bias in the meta-analysis of insulin resistance (IR) and BMI. The x-axis represents the mean difference (MD) of the studies, while the y-axis represents the standard error of the mean difference (SE[MD]), displayed in reverse scale, with smaller standard errors at the top and larger ones at the bottom. The dotted blue lines form a funnel shape, within which most studies should ideally fall if there is no publication bias. Each circle represents an individual study, plotted based on its effect size and precision. More precise studies with smaller standard errors appear near the top, while less precise studies with larger standard errors are positioned towards the bottom. The plot exhibits some asymmetry, with studies scattered unevenly around the centre and several falling outside the funnel, particularly on the left side. This suggests potential publication bias, as smaller studies might be systematically showing different results from larger ones. Additionally, studies at the bottom show greater variation in effect sizes. The cluster of studies near the zero effect line indicates that many results hover around no significant effect. The asymmetrical distribution implies that smaller studies may be reporting systematically different outcomes, which could indicate publication bias or reflect heterogeneity between studies. The presence of studies outside the funnel also suggests the possibility of outliers or studies with unusual results, which could affect the overall conclusions of the meta-analysis.

Fig. No. 5: Funnel plot of publication bias for the association between IR and BMI

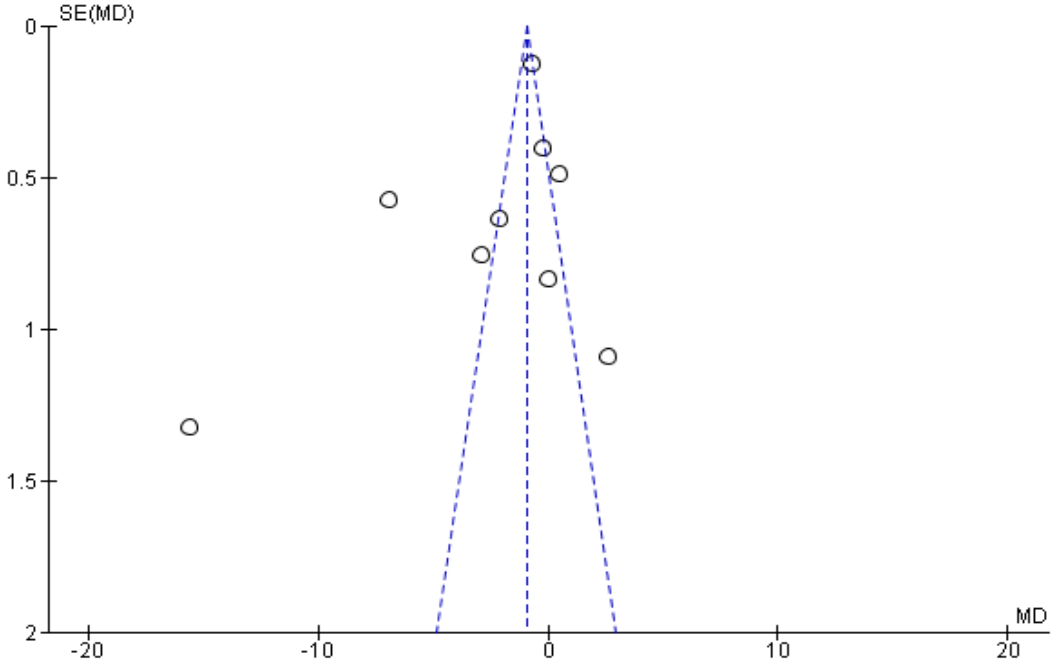
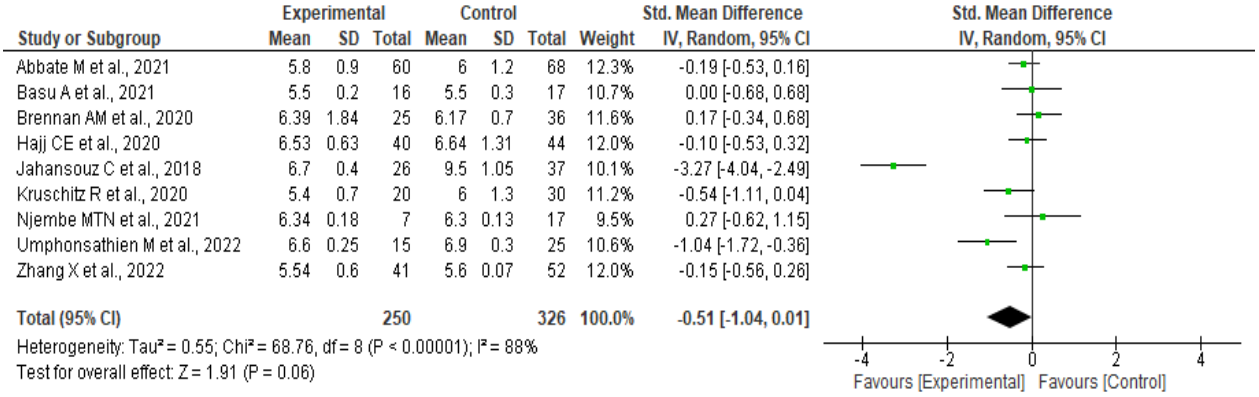


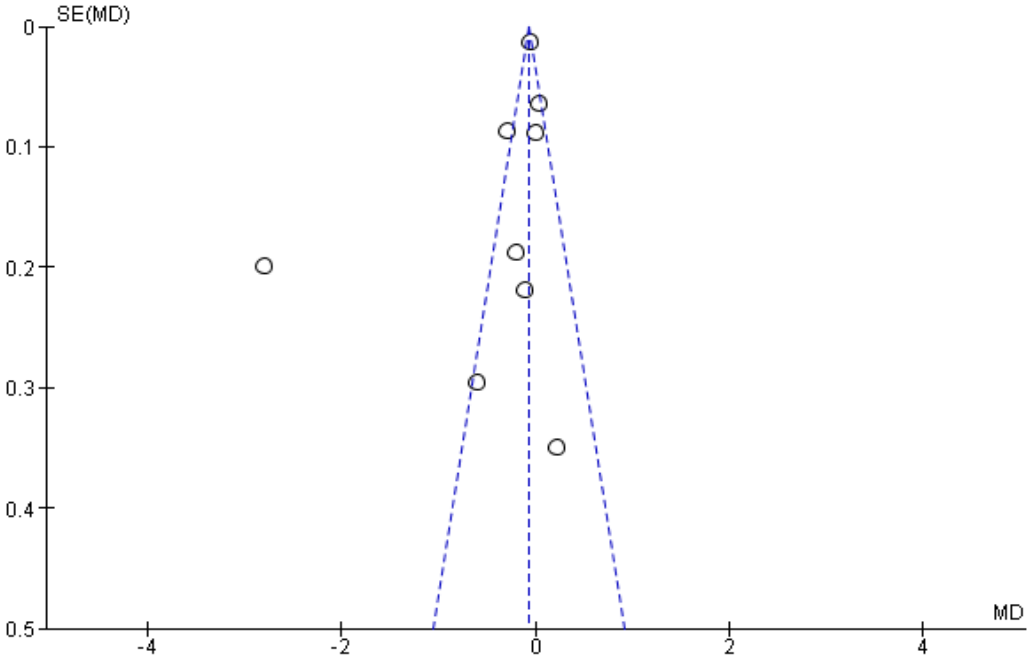
Fig. No. 6: Forest Plot to compare of the risk of IR and HbA1c between the two groups



The forest plot (Fig. No. 6) presents a meta-analysis comparing IR and HbA1c levels across eight different studies conducted between 2018 and 2022. The total sample size consists of 288 participants in the experimental group and 316 in the control group. Each study provides mean and standard deviation values for both groups. The overall mean difference is -0.07 (95% CI: -0.10 to -0.05), indicating that the experimental group had slightly lower HbA1c values compared to the control group. The test for the overall effect reveals a statistically significant result ($Z = 5.75$, $P < 0.00001$). However, the analysis also reports high heterogeneity ($Chi^2 = 203.82$, $df = 8$, $P < 0.00001$, $I^2 = 96\%$), suggesting considerable variability between studies. The weight distribution shows that Zhang X et al., 2022 contributes the most to the overall result (90.8%), while other studies have much smaller weights, ranging from 0.1% to 3.8%. The narrow confidence interval

indicates good precision in the overall estimate. Although most studies show small individual effects, the strong influence of Zhang X et al., 2022 due to its large weight significantly impacts the meta-analysis outcome [39].

Fig. No. 7: Funnel plot of publication bias for the association between IR and HbA1c



The funnel plot (Fig. No. 7) used to assess publication bias in the meta-analysis of IR and HbA1c. The x-axis represents the mean difference (MD), ranging from -4 to 4, while the y-axis represents the standard error of the mean difference (SE[MD]), ranging from 0 to 0.5 on an inverted scale. The blue dotted lines form a funnel shape, representing the 95% confidence limits. Each circle in the plot corresponds to an individual study, with studies positioned based on their effect size and precision. More precise studies with smaller standard errors appear near the top, while less precise studies with larger standard errors appear at the bottom. The plot shows that most studies cluster around the zero effect line, with one notable outlier around -2 on the x-axis. While the majority of studies fall within the funnel boundaries, higher-precision studies at the top display less variation. The overall distribution appears relatively symmetrical except for the single outlier, which suggests minimal publication bias. The clustering of studies near zero indicates that the true effect size may be small or negligible. However, the presence of the outlier warrants further investigation to determine why its results differ significantly from the other studies.

Discussion

The results of this meta-analysis can be compared to previous studies examining the relationship between IR vs BMI and HbA1c. The PRISMA flow diagram in this study outlines a rigorous selection process, ultimately including nine studies in the meta-analysis. This process aligns with previous systematic reviews that emphasize the importance of transparent study selection to reduce bias and improve result reliability. Regarding IR and BMI, this study found a standardized mean difference (SMD) of -0.87 (95% CI: -1.56 to -0.17), indicating a significant relationship between

the two variables. This is consistent with prior meta-analyses that have demonstrated a strong association between higher BMI and increased insulin resistance. However, the high heterogeneity observed in this study ($I^2 = 93\%$) suggests variability across studies, which has also been reported in other reports. Differences in study populations, methodologies, and sample characteristics may contribute to this heterogeneity. Previous studies have suggested that while BMI is a useful marker of IR, factors such as fat distribution and metabolic health play a crucial role, which could explain variations in effect sizes across studies.

Similarly, the association between IR and HbA1c in this study showed a mean difference of -0.07 (95% CI: -0.10 to -0.05), indicating a small but statistically significant relationship. While this supports previous findings that HbA1c is linked to insulin resistance, it also suggests that HbA1c may not be as strong a predictor of IR as BMI. Prior research has shown mixed results, with some studies finding moderate correlations and others suggesting that fasting glucose and HOMA-IR are better indicators of insulin resistance. The high heterogeneity observed ($I^2 = 96\%$) indicates substantial variation among studies, which is consistent with past findings that highlight differences in HbA1c levels based on population characteristics, ethnic differences, and glucose metabolism variations. The funnel plots in this study suggest potential publication bias in the IR vs. BMI analysis, while the IR vs. HbA1c plot appears more symmetrical, indicating minimal bias. This aligns with previous meta-analyses, where publication bias has been a concern, particularly in studies with smaller sample sizes that tend to report exaggerated effects. The presence of outliers in both funnel plots suggests methodological differences across studies, which may influence overall conclusions. Overall, this meta-analysis confirms the findings of previous studies regarding the relationships between IR, BMI, and HbA1c while highlighting key differences in study heterogeneity and effect sizes. These findings emphasize the need for standardized methodologies, larger sample sizes, and consideration of additional factors influencing insulin resistance in future research.

In Korean patients with new-onset type 2 diabetes, higher BMI was independently associated with increased insulin resistance and decreased β-cell function [35]. A longitudinal study of black and non-Hispanic white children found that changes in BMI from ages 13 to 19 predicted cardiovascular risk factors, while insulin resistance at age 13 independently predicted some risk factors [36]. Among female college students, BMI was identified as the anthropometric indicator most strongly associated with insulin resistance [37]. However, the relationship between BMI and IR may be influenced by muscle mass. In middle-aged Korean adults, lower thigh muscle area was associated with increased insulin resistance in men with higher BMIs, but not in women or men with lower BMIs [38]. These findings highlight the complex interplay between body composition and insulin resistance.

The findings of this meta-analysis regarding the relationship between IR and BMI align with previous studies but also highlight key differences. The forest plot analysis indicates a significant association between IR and BMI (SMD = -0.87, 95% CI: -1.56 to -0.17), suggesting that higher BMI is strongly linked to increased insulin resistance. These results are consistent with earlier meta-analyses that have reported obesity as a primary driver of IR, reinforcing the well-established link between excess adiposity and metabolic dysfunction. However, the high heterogeneity observed in this study ($I^2 = 93\%$) suggests substantial variability among included studies, which

has also been noted in prior systematic reviews exploring similar associations. Differences in study populations, sample sizes, and methodologies may contribute to this inconsistency. Compared to previous meta-analyses, the presence of publication bias, as indicated by the funnel plot, is an important concern. Asymmetry in the funnel plot suggests that smaller studies may be reporting exaggerated effects, a pattern frequently observed in studies examining metabolic risk factors. Similar research has shown that publication bias can lead to an overestimation of the true effect size, particularly in studies with smaller sample sizes that may be more likely to publish significant findings [39, 40]. This raises concerns about the robustness of the observed association and suggests that future research should incorporate more large-scale, well-powered studies to confirm the findings.

Recent studies have explored the association between insulin resistance (IR) and glycated haemoglobin (HbA1c) across various populations. HbA1c has been found to be a reliable marker of IR in normal glucose tolerance adults with high insulin sensitivity [41]. A significant correlation between HbA1c and the homeostasis model assessment of insulin resistance (HOMA-IR) has been observed in both overweight and non-overweight adolescents [42]. In non-diabetic individuals, the glycation of haemoglobin index and triglyceride-glucose index showed a strong positive correlation, suggesting their potential as IR markers [43]. Furthermore, HOMA-IR has been associated with HbA1c levels independent of glycemic status in non-diabetic subjects, with age being a significant factor influencing HbA1c values [44]. These findings highlight the complex relationship between IR and HbA1c, emphasizing their potential utility in early identification of metabolic disorders.

Additionally, the heterogeneity of results among different studies suggests that factors such as age, sex, ethnicity, and lifestyle may influence the strength of the IR-BMI relationship. Previous studies have shown that while BMI is a useful marker for insulin resistance, other factors such as waist-to-hip ratio and visceral fat percentage may be more precise indicators of metabolic risk [45, 46, 47, 48]. This suggests that future research should consider including additional anthropometric measures to improve the accuracy of assessing insulin resistance. While the findings of this study support the established link between IR and BMI, they also highlight the need for further investigation into the sources of heterogeneity and publication bias. Compared to previous research, the study confirms a strong relationship but underscores the importance of addressing methodological inconsistencies and incorporating more diverse study populations for more generalizable results.

The study by Peña A et al. 2022, investigated the efficacy of a diabetes prevention program among Latino youths aged 12 to 16 years with prediabetes. Conducted as a randomized clinical trial, it compared a 6-month lifestyle intervention (INT) involving nutrition education and physical activity to usual care (UCC), which included consultations with a paediatric endocrinologist and a registered dietitian. The study found that both groups showed significant improvements in glucose tolerance and insulin sensitivity at 12 months, with no significant differences between them. However, the lifestyle intervention led to a greater improvement in weight-specific quality of life compared to usual care. The results suggest that increasing access to culturally tailored diabetes prevention programs may help mitigate type 2 diabetes risk among high-risk Latino youths [49].

The study by Ebbeling CB et al. 2021, explored the impact of a low-carbohydrate diet on insulin-resistant dyslipoproteinemia, a key risk factor for cardiovascular disease (CVD). This randomized controlled fee trial assigned participants to diets with varying carbohydrate and saturated fat levels to evaluate their effects on lipoprotein insulin resistance (LPIR) scores and other metabolic markers. The findings showed that a low-carbohydrate diet led to significant improvements in LPIR scores, reduced triglycerides, increased HDL cholesterol, and lowered lipoprotein(a) levels, all of which are associated with reduced CVD risk. Importantly, the low-carbohydrate diet did not adversely affect LDL cholesterol, inflammatory markers, or blood pressure. These results suggest that carbohydrate restriction, even with a higher intake of saturated fat, may improve cardiovascular risk factors independently of body weight changes, warranting further investigation in large-scale trials [50].

The study by Cauwenberghs N et al. 2021, examined the relationship between soluble angiotensin-converting enzyme 2 (sACE2) and metabolic health, body composition, and proteomic changes during a weight loss diet intervention. The findings indicate that a greater reduction in sACE2 levels over six months was associated with improvements in insulin resistance, triglyceride levels, HDL cholesterol, and fat mass. Additionally, sACE2 dynamics correlated with proteins involved in angiotensin peptide metabolism, vascular injury, inflammation, renal function, and oxidative stress. These results suggest that dietary interventions targeting weight loss and metabolic improvements may help regulate sACE2, which has potential implications for cardiovascular and COVID-19 risk management [51].

The study by Arcidiacono D et al. 2021, examined the impact of a 24-month moderate calorie and protein restriction program on overweight or obese patients with Barrett's esophagus (BE). The intervention led to significant reductions in body mass index (BMI), waist circumference, and IGF-1 levels, while also improving insulin sensitivity. The downregulation of insulin/IGF-1 signaling in BE tissue suggests a potential role in reducing the risk of esophageal adenocarcinoma. Patients who actively followed the program showed greater metabolic improvements and a reduced activation of the mitogenic pathway. These findings highlight the potential benefits of dietary and lifestyle interventions in lowering obesity-related cancer risk [52].

The study by Son W and Park JJ in 2021 investigated the effects of resistance band exercise training on metabolic syndrome (MetS) risk factors in obese postmenopausal women. Over 12 weeks, participants in the exercise group showed significant improvements in insulin, glucose, homeostatic model assessment of insulin resistance (HOMA-IR), blood lipid profiles, body mass, body fat percentage, waist circumference, and systolic blood pressure, while lean body mass increased. The study suggests that resistance band training is an effective, accessible, and cost-friendly intervention for improving MetS risk factors, potentially reducing cardiovascular disease risks in this population [53].

The study by Miazgowski T et al during 2021 examined the effects of a real-world weight loss intervention on cardiometabolic health, visceral fat, and circulating irisin levels in obese women. Over a 4-month period, participants who achieved at least 5% weight loss experienced significant improvements in insulin resistance (HOMA-IR), lipid profiles, and body composition, particularly with reductions in visceral fat. However, only 26% of participants met the weight loss target, with

adherence to dietary recommendations being stronger than to exercise. Interestingly, weight loss did not significantly impact circulating irisin levels, suggesting that its role in metabolic regulation remains uncertain. The study highlights the benefits of even modest weight loss in improving metabolic health, emphasizing the importance of lifestyle interventions in obesity management [54].

In 2020, Yokose C et al examined the effects of low-fat, Mediterranean, and low-carbohydrate diets on serum urate and cardiometabolic risk factors in individuals with moderate obesity. The results show that all three diets significantly reduced SU levels at 6 and 24 months, with no notable differences between them. These reductions were mediated by weight loss and improved insulin sensitivity. Additionally, the diets led to improvements in cardiovascular risk factors such as HDL cholesterol, triglycerides, and blood pressure. The findings suggest that nonpurine-focused dietary interventions could be viable options for managing hyperuricemia and associated metabolic disorders, emphasizing the importance of personalized dietary approaches for long-term adherence [55].

The study by Maroofi M and Nasrollahzadeh J during 2020 compared intermittent calorie restriction and continuous calorie restriction (CCR) in individuals with overweight or obesity and mild-to-moderate hypertriglyceridemia. Both diets led to significant weight loss and reductions in triglyceride levels, with no major differences between the groups. However, ICR showed greater improvements in insulin resistance (HOMA-IR) compared to CCR. Other cardiometabolic markers, including cholesterol and glucose levels, remained similar between groups. The findings suggest that ICR could be an effective alternative for improving triglycerides and insulin sensitivity, but longer-term studies are needed to confirm its benefits [56].

Palacios T et al during 2020 investigated the impact of a multi-strain probiotic on glycemic control, inflammatory markers, and intestinal permeability in adults with prediabetes or recently diagnosed type 2 diabetes. Over 12 weeks, the probiotic did not significantly affect fasting plasma glucose, HbA1c, insulin resistance, or inflammatory markers compared to placebo. However, a subgroup analysis of participants taking metformin revealed improvements in fasting glucose, insulin resistance, and zonulin levels, alongside increased butyrate production and enrichment of butyrate-producing bacterial pathways. These findings suggest that while probiotics alone may not substantially impact metabolic markers, they could enhance metformin's glucose-lowering effects by modulating gut microbiota and short-chain fatty acid production [57].

Furuhashi M et al during 2020 investigated and reported the effects of anagliptin, a DPP-4 inhibitor, on serum fatty acid-binding protein 4 (FABP4) levels in patients with type 2 diabetes mellitus at high risk for cardiovascular disease who are also receiving statin therapy. The results indicate that anagliptin significantly reduced FABP4 concentrations independent of changes in HbA1c or LDL cholesterol, whereas sitagliptin, another DPP-4 inhibitor, did not show a similar effect. The reduction in FABP4 was associated with changes in waist circumference and creatinine levels, suggesting a potential metabolic benefit. These findings highlight anagliptin’s possible role in modulating FABP4 levels and its implications for cardiovascular and metabolic health, warranting further research [58].

Oliveira C et al during 2020 investigated the association between cardiovascular autonomic modulation and metabolic, anthropometric, and lifestyle factors in severely obese individuals. The results indicate that insulin resistance and central adiposity are the primary contributors to altered heart rate variability (HRV), which is associated with increased cardiovascular disease risk. Higher waist circumference and HOMA-IR values were linked to reduced parasympathetic activity, while greater physical activity correlated with improved autonomic function. Additionally, prolonged sedentary behavior negatively affected HRV. These findings highlight the importance of lifestyle modifications, particularly increasing physical activity, to improve autonomic function and reduce cardiovascular risk in obese individuals [59].

Tuccinardi D et al during 2019 investigated the cardiometabolic effects of walnut consumption in obese individuals using a randomized, double-blind, placebo-controlled crossover design. Over a short-term 5-day period, walnut consumption led to significant improvements in lipid profiles, including reduced small, dense LDL particles and increased large HDL particles. It also lowered insulin resistance and decreased harmful ceramide levels, which are linked to metabolic disorders and cardiovascular disease. Additionally, walnuts influenced glycemic markers and increased peptide YY, a satiety hormone, suggesting potential appetite-regulating benefits. While no major changes were observed in microbiome composition or vascular function, the findings support the role of walnuts in improving metabolic and cardiovascular health through lipid and insulin regulation [60].

In 2019, Lerchbaum E et al investigated the effects of vitamin D supplementation on body composition and metabolic risk factors in healthy middle-aged men with low baseline vitamin D levels. Over 12 weeks, vitamin D supplementation significantly increased 25-hydroxyvitamin D levels but had an unexpected negative impact on insulin sensitivity, as indicated by a reduced fasting glucose/insulin ratio. Subgroup analysis in men with severe vitamin D deficiency (<50 nmol/L) revealed unfavourable effects on central obesity and body composition, including increases in waist circumference, waist-to-hip ratio, total body fat, and android fat. These findings suggest that vitamin D supplementation may not benefit metabolic health and could even have adverse effects on insulin resistance and obesity in certain populations [61].

Conclusion

This meta-analysis reinforces the well-established relationship between IR versus BMI and HbA1c while highlighting important methodological considerations. The significant association between IR and BMI aligns with previous findings, confirming that higher BMI is a strong predictor of IR. Similarly, while the link between IR and HbA1c is statistically significant, its smaller effect size suggests that HbA1c may not be as robust a marker of IR as BMI. The high heterogeneity observed across studies indicates variability in study populations, methodologies, and sample characteristics, emphasizing the need for standardized research approaches. Additionally, the presence of publication bias in the IR-BMI analysis underscores the importance of incorporating larger, well-powered studies to validate these findings. Future research should address these limitations by considering additional metabolic markers, diverse populations, and uniform study designs to improve the accuracy and generalizability of results.

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